SMF
Forum Médical Suisse
Schweizerisches Medizin-Forum
FMS
Swiss Medical Forum

7.5.2008

Supplementum 40

ad Swiss Medical Forum
2008;8(18–19)

76e Assemblée annuelle de la Société Suisse de Médecine Interne

Médecine et Société

Medizin und Gesellschaft

Beaulieu Lausanne, 21–23 mai 2008

EMH FMH Schwabe
Editores Medicorum Helveticorum

Offizielles Fortbildungsorgan der FMH **www.medicalforum.ch**
Organe officiel de la FMH pour la formation continue **www.medicalforum.ch**
Bollettino ufficiale per la formazione della FMH **www.medicalforum.ch**

S1–S4	**Communications libres SSMI Session 1: Système de soins** **Freie Mitteilungen SGIM Session 1: Betreuung und Pflege**	**3 S**
S5–S8	**Communications libres SSMI Session 2: Qualité des soins** **Freie Mitteilungen SGIM Session 2: Qualität der Pflege**	**4 S**
S9–S15	**Communications libres SSMI Session 3: Prédiction des risques** **Freie Mitteilungen SGIM Session 3: Risikovorhersage**	**5 S**
S16–S21	**Communications libres SPSG** **Freie Mitteilungen SFGG**	**7 S**
S22–S27	**Communications libres SSMI Session 4: Santé publique** **Freie Mitteilungen SGIM Session 4: Public health**	**9 S**
S28–S31	**Communications libres SSMI Session 5: Stratégie diagnostique** **Freie Mitteilungen SGIM Session 5: Diagnostik**	**11 S**
S32–S35	**Communications libres SSMI Session 6: Stratégie thérapeutique** **Freie Mitteilungen SGIM Session 6: Therapeutisches Vorgehen**	**12 S**
S36–S39	**Communications libres SSMI Session 7: Communication et psychosocial** **Freie Mitteilungen SGIM Session 7: Kommunikation et psychosoziale Aspekte**	**13 S**
S40–S47	**Communications libres SSHé: Clinical Hematology** **Freie Mitteilungen SGH: Clinical Hematology**	**14 S**
S48–S53	**Communications libres SSHé:** **Hemostasis, Vascular Biology and Transfusion Medicine** **Freie Mitteilungen SGH:** **Hemostasis, Vascular Biology and Transfusion Medicine**	**17 S**
S54–S61	**Communications libres SSHé: Experimental Hematology** **Freie Mitteilungen SGH: Experimental Hematology**	**19 S**
SGH1–SGH2	**Prix scientifiques SSHé 2008** **Wissenschaftliche Preise SGH 2008**	**21 S**
P1–P3	**Poster SSMI: Diabétologie** **Posters SGIM: Diabetologie**	**22 S**

IMPRESSUM

Journal officiel de formation continue de la Société Suisse de Médecine Interne

Swiss Medical Forum – Forum Médical Suisse
EMH Editions médicales suisses SA
Farnsburgerstrasse 8, 4132 Muttenz
Tél. +41 (0)61 467 85 55
Fax +41 (0)61 467 85 56
smf@emh.ch, www.medicalforum.ch

Editions
EMH Editores Medicorum Helveticorum
EMH Editions médicales suisses SA
Case postale, 4010 Bâle, www.emh.ch

Rédaction
Prof. Reto Krapf (rédacteur en chef),
Prof. Claude Genton, PD Dr Ludwig T. Heuss,
Prof. Klaus Neftel, Dr Pierre Périat (rédacteur conseil), Prof. Ruedi Ritz (rédacteur conseil),
Prof. Rolf A. Streuli, Prof. Antoine de Torrenté,
Prof. Bruno Truniger, Prof. Peter Tschudi,
Prof. Gérard Waeber

Rédacteur aux éditions
Dr Martin Sonderegger

Coordination
Ruth Schindler

Lectorat
Christiane Hoffmann (français)
Judith Schifferle, lic. phil. (allemand)
Roy Turnill, MA (anglais)

Traduction
Dr Georges-André Berger, Dr Rainer Bielinski,
Dr Thomas Fisch

Production
Schwabe SA, Muttenz

Paraît le mercredi

Annonces
EMH Editions médicales suisses SA
Ariane Furrer
Assistante Placement des annonces
Farnsburgerstrasse 8
CH-4132 Muttenz
Tél. +41 (0)61 467 85 88
Fax +41 (0)61 467 85 56
afurrer@emh.ch

Marketing EMH
Thomas Gierl M.A.
Responsable marketing et communication
Farnsburgerstrasse 8
CH-4132 Muttenz
Tél. +41 (0)61 467 85 49
Fax +41 (0)61 467 85 56
tgierl@emh.ch

ISSN: version imprimée: 1661-6138
version en ligne: 1661-6146

Abonnements membres de la FMH
FMH Fédération des médecins suisses
Elfenstrasse 18
3000 Berne 15
Tél. +41 (0)31 359 11 11
Fax +41 (0)31 359 11 12
fmh@hin.ch

Autres abonnements
EMH Editions médicales suisses, abonnements
Farnsburgerstrasse 8, 4132 Muttenz
Tél. +41 (0)61 467 85 75
Fax +41 (0)61 467 85 76
abo@emh.ch

© 2008 by EMH Editions médicales suisses SA, Bâle. Tous droits réservés. Toute reproduction d'article, y inclus électronique et la traduction, en totalité ou par extrait, est soumise à l'autorisation écrite des éditions.

Avertissement: la rédaction et les éditions EMH déclinent toute responsabilité quant aux indications de posologie et de forme galénique fournies par les auteurs. Celles-ci doivent être vérifiées selon les cas.

P4–P6	**Posters SSMI: Endocrinologie** **Posters SGIM: Endokrinologie**	**23 S**
P7–P19	**Posters SSMI: Métabolisme** **Posters SGIM: Stoffwechsel**	**24 S**
P20–P23	**Posters SSMI: Néphrologie** **Posters SGIM: Nephrologie**	**28 S**
P24–P26	**Posters SSMI: Gastroentérologie** **Posters SGIM: Gastroenterologie**	**29 S**
P27–P28	**Posters SSMI: Hépatologie** **Posters SGIM: Hepatologie**	**30 S**
P29–P35	**Posters SSMI: Communication et psychosocial** **Posters SGIM: Kommunikation und psychosoziale Aspekte**	**31 S**
P36–P39	**Posters SSMI: Systèmes de soins** **Posters SGIM: Betreuung und Pflege**	**33 S**
P40–P60	**Posters SSMI: Maladies cardiovasculaires** **Posters SGIM: Kardiovaskuläre Erkrankungen**	**34 S**
P61–P63	**Posters SSMI: Pneumologie** **Posters SGIM: Pneumologie**	**40 S**
P64–P112	**Posters SSMI: Médecine interne générale** **Posters SGIM: Allgemeine Innere Medizin**	**41 S**
P113–P127	**Posters SSMI: Infectiologie** **Posters SGIM: Infektiologie**	**56 S**
P128–134	**Posters SSMI: Oncologie** **Posters SGIM: Onkologie**	**61 S**
P135–P143	**Posters SSHé: Transplantation Hematology** **Posters SGH: Transplantation Hematology**	**63 S**
P144–P152	**Posters SSHé: Clinical Hematology** **Posters SGH: Clinical Hematology**	**66 S**
P153–P161	**Posters SSHé: Experimental and Laboratory Hematology** **Posters SGH: Experimental and Laboratory Hematology**	**69 S**
P162–P170	**Posters SSHé: Hemostasis and Transfusion Medicine** **Posters SGH: Hemostasis and Transfusion Medicine**	**72 S**
P171–P177	**Posters SPSG** **Posters SFGG**	**75 S**
P178–P191	**Session interactive des posters SPTC** **Interaktive Postersession SKPT**	**77 S**

S1

Accuracy of drug advertisements in Swiss medical journals

Nordmann A. J., Gonzalez Santiago M., Bucher H. C. (Basel)

Background: The accuracy of drug advertisements quoting a reference study in Swiss medical journals is unknown.
Methods: We screened all issues of six Swiss medical journals published in the year 2005 (Swiss Medical Weekly, Swiss Medical Forum, Schweizerische Ärztezeitung, Ars Medici, Therapeutische Umschau, Therapiewoche Schweiz) to identify all drug advertisements for pain killers, gastroenterological and psychopharmacological drugs. Two reviewers then independently evaluated all drug advertisements referring to at least one publication according to prespecified criteria. The pharmaceutical claim was rated as being supported, potentially biased or or not supported by the quoted study according to prespecified criteria. Disagreement between the two reviewers was resolved by consensus. Kappa statistics were calculated to measure the agreement between the reviewers.
Results: We identified 78 claims referring to a published study (32 claims [41%] referred to pain killers, 30 [38%] to psychopharmacological drugs, and 16 [21%] to gastrointestinal drugs. Overall, 53% of all claims were rated to be biased (n = 25, 32%) or not supported (n = 16, 21%) by the quoted reference study. Thirty-seven (47%) claims were supported by the corresponding reference study. The kappa statistics for supported, not supported and potentially biased claims were 0.77, 0.73, and 0.71, respectively, demonstrating substantial agreement between the two reviewers. Studies with potential conflict of interest had a higher probability to support the corresponding claim than studies without identified conflict of interest (62 vs 23% p = 0.001). Similarly, studies funded by the industry had a trend towards a higher probability to support the corresponding claim than studies without information about their financial source (56 vs 34%, p = 0.055).
Conclusions: More than half of all pharmaceutical claims assessed were potentially biased or not supported by the quoted reference study. Physicians need to be aware that they can not blindly trust drug advertisement claims even when they seem to refer to scientific studies.

S2

Inventory and description of disease management programs in Switzerland

Peytremann Bridevaux I., Burnand B.
(Lausanne, Lausanne and Montreal)

Background: Disease management, a system of coordinated health care interventions for populations with chronic diseases in which patient self-care is a key aspect, has been shown to be effective for several conditions. Little is known on the supply of disease management programs in Switzerland.
Objectives: To systematically search, record and evaluate data on existing disease management programs in Switzerland.
Methods: Programs met our operational definition of disease management if their interventions targeted a chronic disease, included a multidisciplinary team and lasted at least 6 months. To find existing programs, we searched Swiss official websites, Swiss web-pages using Google, medical electronic database (Medline), and checked references from selected documents. We also contacted personally known individuals, those identified as possibly working in the field, individuals working in major Swiss health insurance companies and people recommended by previously contacted persons (snow ball strategy). We developed an extraction grid and collected information pertaining to the following 8 domains: patient population, intervention recipient, intervention content, delivery personnel, method of communication, intensity and complexity, environment and clinical outcomes (measures?).
Results: We identified 8 programs fulfilling our operational definition of disease management. Programs targeted patients with diabetes, hypertension, heart failure, obesity, alcohol dependence, psychiatric disorders or breast cancer, and were mainly directed towards patients. The interventions were multifaceted and included education in almost all cases. Half of the programs included regularly scheduled follow-up, by phone in 3 instances. Healthcare professionals involved were physicians, nurses, case managers, social workers, psychologists and dietitians. None fulfilled the 6 criteria established by the Disease Management Association of America.
Conclusions: Our study shows that disease management programs, in a country with universal health insurance coverage and little incentive to develop new healthcare strategies, are scarce, although we may have missed existing programs. Nonetheless, those already implemented are very interesting and rather comprehensive. Appropriate evaluation of these programs should be performed in order to build upon them and try to design a generic disease management framework suited to the Swiss healthcare system.

S3

Adverse drug event rates in six community hospitals in Massachusetts: frequency before implementing computerized physician order entry

Hug B.L., Witkowski D.J., Sox C.M., Keohane C.A., Seger D.L., Yoon C., Matheny M.E., Melin J.A., Bates D.W.
(Basel, Melrose, Boston, Burlington)

Background: Medications represent a major cause of harm and are costly in hospitalized patients, but more is known about these issues in tertiary care hospitals than community hospitals.
Objective: To assess the incidence of adverse drug events (ADEs) in six community hospitals prior to implementing computerized physician order entry (CPOE).
Design: Multicenter, retrospective cohort study.
Setting: Six eastern Massachusetts community hospitals with 135 to 285 beds.
Patients: A random selection of adult patients hospitalized from January, 2005 through August 2006. Main Outcome
Measures: ADEs and preventable ADEs.
Methods: Presence of an ADE using an adaptation of the trigger instrument developed by the Institute for Health Care Improvement. Two independent reviewers assessed the preventability.
Results: Patients with ADEs were older (mean age, 74.6 years, p = 0.04), more often female (60.3%, p <0.001) and were more often Caucasian (96.5%, p = 0.006) than patients without ADEs. Of 841 incidents detected (70.1/100 admissions), 65.8% were near misses (41.6/100 admissions) and 21.4% were ADEs (15.0/100 admissions). Of the ADEs, 75.0% were judged preventable. ADEs were rated as serious in 49.4% and life threatening in 11.7%. Of preventable ADEs, 81.5% were judged preventable by implementation of computerized physician order entry (CPOE).
Conclusions: The incidence of ADEs in these community hospitals admissions was higher than in tertiary referral hospitals, and more ADEs were preventable, mostly through CPOE. These data suggest that CPOE may be beneficial in this setting.

S4

Impact d'un soutien informatique sur le traitement de la douleur aiguë aux urgences

Palhais N., Achour S., Tamchès E., Trueb L., Decosterd I., Yersin B., Hugli O. (Lausanne)

L'oligoanalgésie reste un problème significatif dans les centres d'urgence, malgré les recommandations de pratique clinique (RPC) édictées par de nombreuses sociétés médicales. Or, si une application informatique aide de nombreux centres d'urgences dans leur gestion quotidienne des patients (flux, recueille de données cliniques dont l'intensité de la douleur, etc.), elle n'est que rarement employée comme une aide à la bonne pratique médicale. But de l'étude: déterminer si le développement d'un module informatique spécifiquement dédié à la prise en charge de la douleur améliore le traitement médical de la douleur aiguë aux urgences. Méthode: étude prospective pré- et post-déploiement d'un module informatique activant, lors de l'installation du patient en zones de soins, l'ouverture automatique dans l'application informatique de fenêtres surgissantes (pop-up) diffusant des messages rappelant aux soignants d'évaluer la douleur, à la traiter selon les RPC, et à adapter l'antalgie après réévaluation de la douleur; l'algorithme gérant ces fenêtres est basé sur les RPC de notre service (1); critères d'évaluation de l'intervention: prescription par les médecins et administration d'antalgique en zones de soins. Données recueillies par revue des dossiers médico-infirmiers. Inclusion de tous patient >= 16 ans admis avec une douleur <8 jours ou ayant développé une douleur durant leur séjour aux urgences. Analyses par statistiques descriptives; comparaison pré et post-intervention par test exact de Fisher pour les données catégorielles, par test de t pour échantillons non-appariés pour les données continues; p bilatéral <0,05 indicateur de différences significatives. Résultats: 183 patients inclus dans chacune des phases. Âge moyen (43,8 et 45,3 ans; p = 0,56), proportion de femmes (49 et 45%; p = 0,46), et intensité de la douleur à l'admission par EVA (6,4 et 6,2 cm; p = 0,63). Modification amenée par l'intervention entre les phases pré et post-intervention: amélioration de 60 et 71% des patients recevant une antalgie (p = 0,048); augmentation de 0,98 à 1,38 prescription d'antalgique/patient (p = 0,003) ; augmentation de 8 à 21% de la proportion des patients recevant de la morphine pour des douleurs modérées à sévères (p <0,001). Conclusion: le soutien informatique permet d'améliorer de façon significative la quantité et la qualité de l'antalgie administrée par les médecins lors de douleur aiguë aux urgences.
1 E.Tamchès et al. Swiss Med Wkly. 2007;137:223–7.

S5

Quality assessment in gastroenterology: prospective analysis of early and delayed complications of sphincterotomy at a single center

Sagmeister M., Schelling M., Binek J., Borovicka J., Boller D., Knellwolf C., Meyenberger C. (St. Gallen)

Most studies on endoscopic sphincterotomy (EST) assess only procedure related morbidity and mortality and there is lack for data on delayed complications. Our aim was to assess early and delayed complications of EST in a prospective registry allowing quality control and outcome assessment in our institution.
Methods: All patients with EST were included within a prospective registry (inclusion rate: 100%) over a time period of 2 years (Sept.1, 2005 – Aug. 31, 2007). The registry is part of a multiinstitutional registry and allows outcome comparisons with different hospitals. Procedure related complications were assessed immediately after the examination by the endoscopist. Follow up data were collected two weeks after the procedure by a trained study nurse. Follow up of patients was assessed by the help of a structured questionnaire.
Results: A total of 462 EST were analysed. 95% of EST were successful (cannulation of the intended duct) within the first examination. In 15.8% of all EST a precut sphincterotomy was necessary to cannulate the intended duct. The total complication rate (CR) was 10.4%. We documented severe or moderate pancreatitis in 0.9% of EST, perforations in 1.3% of EST, mild pancreatitis in 5.6% of EST, hemorrhage in 2.2% of EST and cholangitis in 0.4% of EST. We observed a procedure related mortality of 0.43% (2 deaths: 1 patient died of post EST pancreatitis and 1 patient died due to cardiorespiratory insufficiency with multiorgan failure after EST). There was a non-procedure related hospital mortality of 2.38% (11 deaths: mainly patients with end stage cancer disease). The main risk factors for complications of EST were: former ERCP pancreatitis (CR: 66.7%), recent stone passage (CR: 29.2%), sphincter of Oddi dysfunction (CR: 20%), combined sedation with propofol, benzodiazepines and opiates (CR 18.1%), precut sphincterotomy (CR: 19.2%), number and intensity of pancreas duct contrast injections (CR: up to 50% with contrast injections up to the pancreas tail).
Conclusion: The study confirmed a considerable early and delayed procedure related complication rate of EST. We could identify specific risk factors for EST related complications. We conclude that there is a need for permanent quality control and outcome assessment for invasive procedures like EST.

S6

Evolution of diagnostic errors in a primary referral hospital over a ten-year period assessed by autopsy

Hoess C., Moll C., Thurnheer R., Widmer F., Krause M. (Münsterlingen)

The advances in modern imaging techniques and diagnostic laboratory tests allow to obtain detailed information about diseased organs and help to recognize various conditions such as pulmonary embolism, heart failure and myocardial damage. It is not clear, however, whether our diagnostic performance has really improved along with the development of these advances. To answer this question, we compared autopsy findings with pre-mortem main diagnoses over a ten year period and assessed the frequency of diagnostic discrepancies over time.
Results: From January 1997 to December 2006 the autopsy rate was 50.1% resulting in 1035 autopsies. There were 60% males, the mean age at death was 73.1 years. Oncologic and cardiovascular diseases were the most common disorders diagnosed at postmortem exam, followed by infectious and neurological diseases. The overall main diagnosis discrepancy rate was 9.1%. Myocardial infarction, pulmonary embolism, aortic disease and endocarditis were most commonly missed. In cardiovascular diseases errors occurred in 18.7%, followed by infectious diseases in 12.9%, oncology in 3.6% and neurology in 1.8%. The error rate of all diseases categories dropped from 15% in 1997/98 to 6.1% in 2005/06 (Figure). This improvement was mainly due to less erroneous cardiovascular diagnoses which decreased from 33% to 13%. Among the study intervals, patient characteristics, autopsy frequency and diseases categories did not differ signifi-cantly excluding a bias. During the 10 year study period, various cardiovascular diagnostics were introduced at our institution including D-dimer, Troponin T, brain natriuretic peptide, comprehensive doppler-echo studies, multislice-CT and MRI as well as algorithms for thromboembolic diseases and acute coronary syndrome.
Conclusion: In patients who die in the hospital, the diagnostic performance improved significantly over a ten year period. This was mainly due to more accurate diagnoses in cardiovascular diseases. This suggests that the introduction of new cardiovascular biomarkers, imaging techniques and diagnostic algorithms is associated with better diagnostic performance.

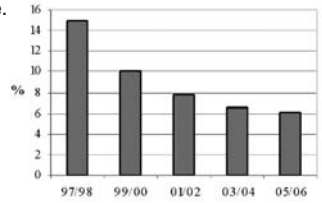


Figure 1
Error rate

S7

Age-related differences in the use of guideline-recommended medical and interventional therapies for acute coronary syndromes: a cohort study

Schoenenberger A.W., Radovanovic D., Stauffer J.-C., Windecker S., Urban P., Eberli F.R., Stuck A.E., Gutzwiller F., Erne P. (Bern, Zürich, Lausanne, Genf, Luzern)

Introduction: Recent guidelines for patients with acute coronary syndromes (ACS) recommend early medical and interventional therapies for older patients. We therefore compared the use of guideline-recommended medical and interventional therapies in older vs. younger patients with ACS.
Methods: In this prospective cohort study, 11932 patients with ACS were enrolled between March 1, 2001, and June 30, 2006 in 55 hospitals in Switzerland. ACS definition included ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). We measured the use of medical and interventional therapies determined after exclusion of patients with contraindications and after adjustment for comorbidities. Multivariate logistic regression models were used to calculate odds ratios (OR) per year increase in age.
Results: Elderly patients were less likely to receive acetylsalicylic acid (OR, 0.976 [95% CI, 0.969–0.980]) or beta-blockers (OR, 0.985 [95% CI, 0.981–0.989]). No age-dependent difference was found for heparin use. Elderly patients with STEMI received less percutaneous coronary interventions (PCI) or thrombolysis (OR, 0.955 [95% CI, 0.949–0.961]). Elderly patients with NSTEMI/UA less often underwent PCI (OR, 0.943 [95% CI, 0.937–0.949]).
Conclusion: Elderly patients across the whole spectrum of ACS were less likely to receive guideline-recommended therapies even after adequate adjustment for comorbidities. Prognosis of elderly patients with ACS may be improved by increasing adherence to guideline-recommended medical and interventional therapies.

S8

"Do not reanimate" (DNR) and "cardio-pulmonary resuscitation" (CPR) orders: descriptive analysis of 206 cases

Elger B.E., Becerra M., Cochet S., Junod Perron N., Hurst S.A. (Genève)

Background: In Switzerland, studies on "Do Not Resuscitate" or "Cardio-Pulmonary Resuscitation" orders (DNR/CPR) are rare. The Clinical Ethics Council of the University Hospital of Geneva (UHG) has issued guidelines on how patient autonomy should be respected in DNR decisions. Consequently, a procedure was implemented in the Internal Medicine Department requiring physicians to specify at patients' admission whether a patient is "DNR" or "CPR" and document the decision on a standardized form in the medical record. This study evaluates how such decisions are made.
Methods: During one year (2004/2005) 206 consecutive cases were obtained in six internal medicine wards: it included four groups according to DNR/CPR status, and whether they were discussed with the patient (dp), or not (ndp). Residents in charge of the patients were interviewed about how the 206 orders were established.
Results: Over 90% of decisions were made within two days of admission. Mean patient age ranged from 63 years for ndp CPR orders to 77 years for dp DNR orders ($p < 0.001$). Ten percent of patients with ndp CPR orders and 41% of patients with ndp DNR orders were incompetent. Two weeks after admission, 18% of patients with ndp DNR orders, and 2–6% of the remaining patients had died ($p = 0.009$). Ndp DNR orders were discussed with the chief resident most often (82%), and ndp CPR orders least often (38%, $p < 0.001$). Orders were rarely (8%) documented in the nursing files. Nurses participated in 7% of the 206 CPR/DNR decisions. Treating physicians were involved in 9%. Family participated in 31% of all DNR decisions, 20% of dp CPR and 6% of ndp CPR orders ($p = 0.004$). For both dp CPR and dp DNR orders, a "real" discussion took place with 87% of the patients. In the other cases patients were only informed. In 95% of dp orders physicians felt it was "good" to have included the patient in the decision. Physicians' comments about the usefulness of the DNR/CPR forms were overall positive.
Conclusions: The DNR/CPR forms help clarify decisions about resuscitation. However, nurses too often remain uninformed of DNR/CPR decisions. Moreover, in many cases residents do not include competent patients in the DNR/CPR decision. Although the UHG ethics council admits some cases for ndp orders regarding competent patients (CPR for patients with good prognosis and DNR orders shortly before death), decision making without including competent patients should remain the exception. Specific training may be useful.

S9

Subclinical thyroid dysfunction is not associated with the risk of coronary heart disease and mortality

Ochs N., Auer R., Bauer D.C., Gussekloo J., Cornuz J., Rodondi N. (Lausanne, San Francisco, Leiden)

Background: Subclinical thyroid dysfunction (defined as abnormal TSH and normal thyroid hormone levels) is common, particularly in older adults and in women, but controversy persists as to whether screening and treatment of subclinical thyroid dysfunction is warranted. As previous studies have been conflicting, we performed a meta-analysis of prospective studies to determine whether subclinical thyroid dysfunction is associated with coronary heart disease (CHD) and mortality (total or cardiovascular).
Methods: We searched MEDLINE from 1950 to June 2007, and the bibliographies of key articles in the field and those included in this review. Two authors independently reviewed each potential study for eligibility and extracted the data. We assessed methodological study quality and performed sensitivity analyses.
Results: 11 prospective studies met our eligibility criteria, 10 examining subclinical hypothyroidism, with 2136 CHD events and 2822 deaths, and 6 examining subclinical hyperthyroidism, with 1399 CHD events and 2021 deaths. Overall, subclinical hypothyroidism was not associated with the risk of CHD (summary relative risk [RR] = 1.20, 95% confidence interval [CI], 0.96–1.49) with weak evidence for heterogeneity (p for heterogeneity = 0.14, I^2 = 33.4%). However, risk estimates were lower when pooling higher quality studies (RR from 1.02 to 1.08). Subclinical hypothyroidism was associated with CHD risk among subjects <65 years (RR for studies with a mean age <65 years = 1.51, 95%CI, 1.09–2.09; vs. 1.05, 95%CI, 0.90–1.22 for studies with a mean age ≥65 years; p for meta-regression by age = 0.02). Results did not meaningfully differ in other sensitivity analyses. Subclinical hypothyroidism was not associated with cardiovascular mortality (RR = 1.18, 95%CI, 0.98–1.42) or total mortality (RR = 1.12, 95%CI, 0.99–1.26). Subclinical hyperthyroidism was not significantly associated with CHD (RR=1.36, 95%CI, 0.92-2.01), cardiovascular mortality (RR = 1.36, 95%CI, 0.86–2.18) or overall mortality (RR = 1.19, 95%CI, 0.95–1.48; for all: p for heterogeneity >0.20, I^2 <30%), but confidence intervals were wider than for subclinical hypothyroidism.
Conclusion: This systematic review of prospective cohort studies with a large number of outcomes included indicates that subclinical hypothyroidism and hyperthyroidism are not associated with CHD risk and mortality, but subclinical hypothyroidism may be associated with increased CHD risk among those <65.

S10

Vascular dysfunction in apparently healthy adolescents conceived by assisted reproductive technologies

Sartori C., Rimoldi S., Bloch J., Duplain H., Stuber T., Kriemler S., Germond M., Nicod P., Allemann Y., Scherrer U. (Lausanne, Bern, Basel)

Environmental influences acting early in life predispose to cardiovascular disease in adulthood. In developed countries, assisted reproductive technologies (ART) account for 1–4% of births. There is growing evidence that the preimplantation mammalian embryo is sensitive to environmental conditions and ART has been found to modulate the epigenome. The safety of ART for long term health is, therefore, of utmost importance, but there is little information. This may be related, at least in part, to the young age of the progeny, since clinically manifest chronic disease may not yet have had time to develop. Hypoxia induces exaggerated pulmonary hypertension and systemic vascular dysfunction in persons displaying endothelial dysfunction. We sought to capitalize on this observation and hypothesized that high-altitude exposure may facilitate the detection of vascular dysfunction in children born after ART. We measured endothelium-dependent vasodilation (high-resolution ultrasound) and vascular stiffness (pulse wave velocity) of the brachial artery, and pulmonary-artery pressure (echo-Doppler) in 20 apparently healthy singletons born from ART (mean age 13 ± 2 y) and 28 age-, sex- and birth weight-matched controls exposed to high-altitude (Jungfraujoch, 3450 m). The major new finding was that healthy adolescents born after ART displayed marked vascular dysfunction both in the systemic and the pulmonary circulation. Brachial artery flow-mediated vasodilation was roughly 30 percent smaller (6.3 ± 1.8 vs. 8.9 ± 1.8%, p <0.001) and pulse wave velocity significantly faster (8.5 ± 2.2 vs. 7.2 ± 1.2 m/s, p = 0.01) in children born after ART than in controls. Similarly, the systolic right ventricular to right atrial pressure gradient was roughly 33 percent higher in offspring of ART than in controls (36 ± 14 vs. 27 ± 7 mm Hg, p = 0.01). This vascular dysfunction was not related to more severe hypoxemia since arterial oxygen saturation was comparable in the 2 groups. These findings demonstrate for the very first time that ART has long lasting effects on vascular function in humans that may predispose to premature cardiovascular disease later in life. We speculate that epigenetic mechanisms may underpin the vascular dysfunction in offspring of ART. If so, the observed vascular dysfunction may not be limited to the present generation of persons born after ART, but could also be transmitted to their progeny. The scientific, societal and ethical challanges at stake here appear tremendous.

S11

Improved prediction of coronary heart disease with markers of atherosclerosis and of inflammation in older adults?

Rodondi N., Marques-Vidal P., Butler J., Cornuz J., Sutton-Tyrrell K., Satterfield S., Ferrucci L., Harris T.B., Vittinghoff E., Bauer D.C., Newman A. (Lausanne, Atlanta, Pittsburgh, Memphis, Bethesda, San Francisco)

Background: Several markers of atherosclerosis and of inflammation have been shown to predict coronary heart disease (CHD) individually. However, the utility of markers of atherosclerosis and of inflammation on prediction of CHD over traditional risk factors has not been well established, especially in the elderly.
Methods: We studied 2202 men and women, aged 70–79, without baseline cardiovascular disease over 6-year follow-up to assess the risk of incident CHD associated with baseline noninvasive measures of atherosclerosis (ankle-arm index [AAI], aortic pulse wave velocity [aPWV]) and inflammatory markers (interleukin-6 [IL-6], C-reactive protein [CRP], tumor necrosis factor-α [TNF-α]). CHD events were studied as either nonfatal myocardial infarction or coronary death ("hard" events), and "hard" events plus hospitalization for angina, or the need for coronary-revascularization procedures (total CHD events).
Results: During the 6-year follow-up, 283 participants had CHD events (including 136 "hard" events). IL-6, TNF-α and AAI independently predicted CHD events above Framingham Risk Score (FRS) with hazard ratios [HR] for the highest as compared with the lowest quartile for IL-6 of 1.95 (95%CI: 1.38–2.75, p for trend <0.001), TNF-α of 1.45 (95%CI: 1.04–2.02, p for trend 0.03), of 1.66 (95%CI: 1.19–2.31) for AAI 0.9, as compared to AAI 1.01-1.30. CRP and aPWV were not independently associated with CHD events. Results were similar for "hard" CHD events. Addition of IL-6 and AAI to traditional cardiovascular risk factors yielded the greatest improvement in the prediction of CHD; C-index for "hard"/total CHD events increased from 0.62/0.62 for traditional risk factors to 0.64/0.64 for IL-6 addition, 0.65/0.63 for AAI, and 0.66/0.64 for IL-6 combined with AAI. Being in the highest quartile of IL-6 combined with an AAI 0.90 or >1.40 yielded an HR of 2.51 (1.50–4.19) and 4.55 (1.65–12.50) above FRS, respectively. With use of CHD risk categories, risk prediction at 5 years was more accurate in models that included IL-6, AAI or both, with 8.0, 8.3 and 12.1% correctly reclassified, respectively.
Conclusions: Among older adults, markers of atherosclerosis and of inflammation, particularly IL-6 and AAI, are independently associated with CHD. However, these markers only modestly improve cardiovascular risk prediction beyond traditional risk factors.

S12

Oxidative stress induced fetal programming of hypoxic pulmonary hypertension

Bloch J., Jayet P-Y., Duplain H., Schwab M., Dessen P., Monney A., Mathieu C., Tolsa J-F., Sartori C., Scherrer U. (Lausanne)

The long term prognosis of pulmonary hypertension remains poor, and its pathogenesis remains incompletely understood. In line with Barker's concept of a fetal programming of adult disease, preeclampsia predisposes the offspring to pulmonary endothelial dysfunction and exaggerated hypoxic pulmonary hypertension later in life, but the underlying mechanisms remain unknown. In women suffering from preeclampsia, reactive oxygen species (ROS) are elevated and contribute to endothelial dysfunction and arterial hypertension. We hypothesized that ROS may pass the placental barrier and induce endothelial dysfunction in the developing pulmonary vasculature of the fetus that may predispose to a pathologic response later in life. To test this hypothesis, C57/Bl6 mice were put on a restrictive diet (75% of normal food intake) during the last 2 weeks of pregnancy, a condition known to induce exaggerated oxidative stress during pregnancy.

Adult male offspring of restricted diet pregnancy were kept in hypoxic cages (FiO_2, 12.5%) for 2 weeks. Mice were then sacrificed, and the main pulmonary arteries were dissected. The pulmonary artery rings were suspended in organ chambers for the measurement of endothelium-dependent pulmonary vasodilation (cumulative dose-response to acetylcholine, 10-8–10-4 mol/L). We found that pulmonary vasodilatation to acetylcholine was markedly impaired in offspring of restrictive diet pregnancies when compared to control mice (ANOVA p <0.0001). Pulmonary-artery endothelial dysfunction was associated with increased oxidative stress, as evidenced by a roughly 50% increase of the TBARS plasma concentration (50.9 ± 3.1 vs. 33.4 ± 5.1 nmol/ml, P <0.01, restrictive diet vs. controls). To test for the pathogenic role of oxidative stress in this setting, we examined the effects of the addition of the antioxidant Tempol (10-4 M) on pulmonary artery responsivness in vitro. Tempol completely restored the pulmonary-artery vasodilatation in vitro (ANOVA p <0.0001). Most importantly, we also found that administration of Tempol (10-2 M in the drinking water) during restrictive diet pregnancy completely prevented pulmonary endothelial dysfunction in the offspring. These data provide the first evidence for a fetal programming of exaggerated hypoxic pulmonary hypertension in mice. The pulmonary endothelial dysfunction in the offspring is induced by increased oxidative stress because administration of an antioxidant prevented this pathologic response.

S13

Are the guidelines appropriate to the cardiovascular risk stratification among women before 66-year in Switzerland?

Berthoud M., Depairon M., Stauffer I., Darioli R. (Lausanne)

The primary prevention of cardiovascular diseases (CVD) is based on the individual risk assessment by using Framingham and similar algorithms derived mainly from European or US male populations. The purpose of this prospective study was to compare the appropriateness of three different common guidelines for cardiovascular risk stratification when using subclinical-atherosclerosis as a surrogate of CV risk. The study population included 560 women (W), aged from 20 to 65 years, non diabetic and without established CVD, who were consecutively were referred to our Lipid Clinic for therapeutic advices. CV- risk factors were systematically screened for each subject, including medical history, physical examination and clinical chemistry. Their estimated 10-year CV-risk assessment was obtained by using the guidelines of Swiss-AGLA (AGLA), NCEP-ATP-3 (ATP-3) and 3th JES-ESC (ESC) guidelines (GL). B-mode ultrasounds on carotid and femoral arteries was performed to detect atherosclerotic plaques (focal thickening of intima-media >1.2 mm). W with plaques on >2 carotid and/or femoral sites were considered as high CV risk (HR). The proportions of W stratified as high 10-year CV-risk by the GL were the following: 5% (AGLA), 2% (ESC) and 24% (ESC). The comparative values (area under the ROC-curve, 95% IC) of GL to detect the 160 HR-W with subclinical atherosclerosis (29%) was significantly higher for AGLA-GL (0.7869, 0.75–0.82) than for ATP-3-GL (0.75, 0.71–0.79) or than for ESC-GL (0.73, 0.68–0.77).
In conclusion, the results suggest that current AGLA-GL recommended by the Swiss Society of Cardiology are the most appropriate to identify HR-W requiring more intensive therapy for the primary prevention of CVD.

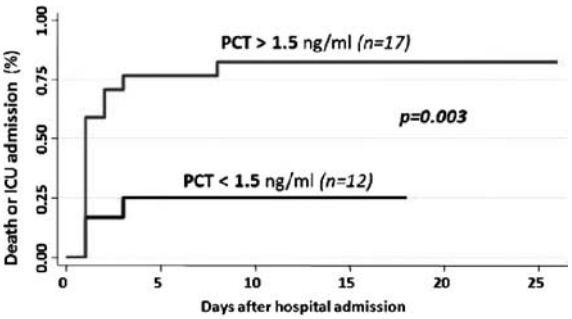
S14

Prognostic value of procalcitonin in Legionella pneumonia

Haeuptle J., Zaborwsky R., Fiumefreddo R., Trampuz A., Steffen I., Frei R., Christ-Crain M., Müller B., Schuetz P. (Basel)

Background: The diagnostic reliability and prognostic implications of procalcitonin (PCT) on admission in patients with community-acquired pneumonia (CAP) due to Legionella pneumophila are unknown.
Patients and methods: We retrospectively analyzed PCT values in 29 patients with microbiologically proven Legionella-CAP admitted to the University Hospital in Basel, Switzerland, between 2002 and 2007 and compared them to other markers of infection, namely C-reactive protein (CRP) and leukocyte count, and two prognostic severity assessment scores (PSI and CURB65).
Results: Laboratory analysis demonstrated that PCT values on admission were >0.1 ng/ml in over 93%, >0.25 in over 86% and >0.5 in over 82% of patients with Legionella-CAP. Patients with adverse medical outcomes (59%, n = 17) including need for ICU admission (55%, n = 16) and/or inhospital mortality (14%, n = 4) had significantly higher median PCT values on admission (4.27 (IQR 2.46–9.48) vs 0.97 (IQR 0.29–2.44, p = 0.01), while CRP values (282 (IQR 218-343, p = 0.28) vs 201 (IQR 147–279, p = 0.28) and leukocyte counts (12 (IQR 10–21) vs 12 (IQR 9–15), p = 0.58) were similar. In receiver operating curves, PCT concentrations on admission had a high prognostic accuracy (AUC 0.78 (95%CI 0.61–96) as compared to CRP (0.61 (95%CI 0.39–0.84, p = 0.19), leucocyte count (0.57 (95%CI 0.35-0.78, p = 0.12), the PSI (0.72 (95%CI 0.52-0.91, p = 0.23) and the CURB65 score (0.58 (95%CI 0.36–0.80, p = 0.18). Kaplan Meier curves (Figure 2) demonstrated that patients with PCT values above the optimal cut off of 1.5ng/ml had a significantly higher risk of adverse outcome above (p = 0.003).
Conclusion: In patients with community-acquired pneumonia due to Legionella pneumophila, PCT levels on admission values could be an interesting predictor for adverse medical outcomes.

Figure 2



S15

The Pulmonary Embolism Severity Index (PESI): prospective validation of a clinical prognostic model for pulmonary embolism

Donzé J., Cornuz J., Righini M., Perrier A., La Gal G., Roy P.M., Sanchez O., Verschuren F., Meyer G., Aujesky D. (Lausanne, Genève, Brest, Angers, Paris, Bruxelles)

Background: Using data from U.S. patients, we previously derived the Pulmonary Embolism Severity Index (PESI), a clinical prognostic model that accurately identifies patients with pulmonary embolism (PE) who are at low-risk of mortality and who are potential candidates for outpatient care. Our objective was to externally validate the PESI in a European patient sample with PE.
Methods: We prospectively validated the PESI in 357 patients objectively diagnosed with PE at 6 European emergency departments. All patients received an initial treatment with heparin, followed by a vitamin K antagonist for at least 3 months. We used baseline data for the model's 11 prognostic variables to stratify patients into 5 risk classes (I–V) of increasing risk of mortality. The study outcome was overall mortality at 3 months after presentation. We calculated the proportion of patients classified as low-risk (classes I and II) based on the PESI. To assess the accuracy of the PESI to predict overall mortality, we estimated the sensitivity, specificity, predictive values and likelihood ratios for low (risk classes I and II) versus higher-risk patients (risk classes III–V). We assessed the discriminatory power of the PESI to predict overall mortality using the area under the receiver operating characteristic curve.
Results: Overall mortality was 5.9% (21/357). Fifty-two per cent of patients (186/357) were classified as low-risk (PESI classes I and II). Low-risk patients had a mortality of only 1.1% (2/186). When dichotomized as low (classes I and II) versus higher-risk (classes III–V), the PESI had a high sensitivity (91%, 95% confidence interval [CI]: 71–97%) and a very high negative predictive value (99%, 95% CI: 96–100%) and negative likelihood ratio (0.20, 95% CI: 0–0.70) for predicting overall mortality. Because this cutoff point was specifically chosen to identify low-risk patients (i.e. to rule out short-term mortality), the specificity (55%, 95% CI: 49–60%) and the positive predictive value (11%, 95% CI: 7–17%) were low. The area under the receiver operating characteristic curve for overall mortality was 0.78 (95% CI: 0.70–0.86).
Conclusions: The PESI reliably identifies low-risk patients with PE who are potential candidates for outpatient treatment or a brief hospital stay. The effectiveness and safety of an outpatient treatment strategy of low-risk patients based on the PESI should be evaluated in a randomized trial.

S16

L'hypoglycémie du sujet âgé diabétique: une maladie silencieuse?

Dr M. Coutaz, Dr J. Morisod (St-Maurice)

Introduction: Le vieillissement entraîne une modification des réponses de contre-régulation à l'hypoglycémie, amenant une symptomatologie peu spécifique (faiblesse, vertiges, confusion) attribuée à tort à d'autres co-morbidités de type neurologique ou psychiatrique, sous-estimant probablement la fréquence des épisodes d'hypoglycémie.
Méthode: Afin de mieux évaluer ce risque nous avons inclus prospectivement 100 patients volontaires diabétiques, au bénéfice d'un traitement d'antidiabétiques oraux et/ou d'Insuline, hospitalisés dans un service de gériatrie aiguë.
5 mesures de glycémie capillaire (07 h – 11 h – 17 h – 22 h – 03 h) ont été effectuées dans les premières 24 h du séjour hospitalier, sans aucune modification du traitement habituel. L'hypoglycémie était définie par une valeur de glycémie inférieure à 4 mmol/l.
Résultats: L'incidence de survenue d'une hypoglycémie s'est révélée très élevée, de l'ordre de 24% pendant les premières 24 h d'hospitalisation. 24 patients ont présentés 33 épisodes d'hypoglycémie (glycémie la plus basse: 1,9 mmol/l), dont le tiers survient à 3 h du matin. Les facteurs de risques habituels d'hypoglycémie décrits chez la personne âgée (insulinothérapie, âge avancé, insuffisance rénale, polymédication, fragilité) n'ont aucune valeur prédictive significative selon les résultats de notre étude (cf. tableau). Par ailleurs, ni l'adjonction d'un médicament au pouvoir hypoglycémiant (acide acétylsalicylique, acenocoumarol, cotrimoxazole, tricyclique), ni le suivi d'un régime antidiabétique n'ont constitué un indice prédictif valable de survenue d'une hypoglycémie.
Conclusion: Selon les résultats de notre étude, les facteurs de risque habituels décrits sont insuffisants pour aider au dépistage de l'hypoglycémie du diabétique âgé traité, qui court un risque sérieux d'hypoglycémie lors de chaque hospitalisation (1/4 des patients de notre collectif). L'absence de symptômes clairement individualisables et le manque d'outils de dépistage nous incitent à recommander des profils glycémiques serrés, incluant la glycémie nocturne, lors de toute hospitalisation.
Tableau

Caractéristiques	Total des patients (N = 100)	Sans hypoglycémie (N =76)	Avec hypoglycémie (N = 24)	Valeur du p
Age	79,29 ± 7,1	79,66 ± 7,1	78,13 ± 6,8	0.35
Score MMS	24,07 ± 5,15	24 ± 5,35	24,29 ± 4,57	0.80
Indice de Barthel	61,24 ±25,53	60,51 ± 25,98	63,54 ± 24,47	0.61
Taux d'albumine g/l	35,34 ± 4,83	35,30 ±4,81	35,48 ± 5	0.87
Clearance creatinine ml/l	62,07 ± 29,32	62,16 ± 29,27	61,8 ± 30,11	0.96
Médicaments différents / jour	8,37 ± 3,07	8,47 ± 3,17	8,04 ± 2,76	0.52
Traitement				
-Insuline (I)	22 %	59 % (13/22)	41 % (9/22) **	**p= 0.08
-Antidiabétiques Oraux (ADO)	67 %	81 % (54/67)	19 % (13/67) **	
-I + ADO	11 %	82 % (9/11)	18 % (2/11)	
Régime antidiabétique	22 %	59 % (13/22)	41 % (9/22)	0.07

S17

Marital status, living place and income are major determinants of first hip fracture age occurrence

Chevalley T., Guilley E., Herrmann F., Hoffmeyer P., Rapin C.-H., Rizzoli R. (Genève)

We previously reported that the risk of hip fracture was higher in communities with low income, and/or in urban as compared to rural areas. However, the influence of socioeconomic risk factors on the age of first hip fracture has not been specifically analyzed in home-dwelling elderly. Therefore, we investigated the impact of marital status, living place and income on the age at first hip fracture in 2320 home-dwelling women and men aged 50 and older discharged from 1991 to 2000 with a diagnosis of a first hip fracture at the Geneva University Hospital. Income of hip fractured patients corresponded to the median household incomes of the patient's Zip code area at the time of the fracture. These median household incomes were based on the 1990 Census and obtained from the Geneva State statistical office. Age of patients was analyzed by analysis of variance according to gender, marital status (unmarried – single, widowed, divorced – or married), rural/urban residence and 3 income categories of similar numbers of patients with no difference in women/men ratios (<53'170 CHF, 53'170–58'371, ≥58'371). First hip fracture occurs at an earlier age for unmarried men compared to married men (–3.13 year; 95% CI = -5.07– -1.19; p = 0.002) while it occurs at a latter age for unmarried women compared to married women (4.61 year; 95% CI = 3.55–5.67; p = <0.001). Patients from urban areas were younger when sustaining their fractures (-1.63 year; 95% CI = -2.89– -0.38; p = 0.011). As compared to the patients living in areas with the highest income category, hip fractures occurred at an earlier age (–1.36 year; 95% CI = -2.41 – -0.30; p = 0.012) among home-dwelling residents of the lowest income category. Women who sustained a fracture at the earliest age (76.5 years) are married and living in an urban area with the lowest income category while those sustaining a fracture at the latest age (83.8) were unmarried and living in a rural area with the highest income category (7.3 year difference; 95% CI = 4.8–9.8; p <0.001). Men with the worse profile (unmarried and living in urban communities with the lowest income) had a fracture at 73.2 years while those with the best profile (married and living in rural communities with the highest income) were 78.8 years old (5.6 year; 95% CI = 1.4–9.8; p = 0.008). In conclusion, these results indicate that in home-dwelling elderly in Geneva, marital status, living place and income are major determinants of the age at first hip fracture, in a gender-specific way.

S18

Outcomes in elderly patients with proximal femoral or humeral fractures treated in an orthogeriatric rehabilitation unit

Carmona G., Rizzoli R., Ammann P. (Genève)

The benefits of orthogeriatric intervention on recovery following a fracture of the proximal femur in the elderly are well documented. Whilst fractures of the proximal humerus are associated with a marked decrease in functional independence, there is a noticeable lack of literature regarding the influence of orthogeriatic intervention in elderly patients who sustain a proximal humeral fracture. We performed a retrospective observational study in patients admitted to an orthogeriatric unit between 2002 and 2006, with a diagnosis of extra- or intracapsular hip fracture (HIP#, n = 291; mean age 83 ± 7 yrs) or proximal humeral fracture (HUM#, n = 73; mean age 81 ± 7 yrs). The rehabilitation program was administered by an interdisciplinary team, integrating walking/balance exercises, muscle strengthening and daily life-training activities. Functional capacity during rehabilitation was evaluated by the functional independence measure (FIM) at admission, after two weeks, and just prior to discharge (median 33 days). To further evaluate the functional outcomes, we separated the functional motor items (MOTOR FIM) into upper and lower limb items (UPPER and LOWER FIM). Values are means (SD) and differences tested using ANOVA and Student's t-test. At admission, age and all motor functional independence scores were significantly higher in patients with HIP# (83.3 ± 6.9 vs. 81.5 ± 6.9 yrs; p = 0.04, MOTOR 38.2 ± 11 vs. 33.6±11; p = 0.002, UPPER 18.9 ± 4 vs. 12.8 ± 4; p <0.0001 and LOWER FIM 16.6 ± 6 vs. 12.9 ± 4; p <0.0001). At discharge, similar scores were observed for FIM and overall MOTOR FIM in both groups, indicating a positive effect of the rehabilitation program. The effect on both fracture types was observed for UPPER and LOWER FIM, highlighting a global effect of orthogeriatric intervention. The kinetics of functional gain in MOTOR FIM differed between the groups; in the HIP# the functional gain was significantly higher during the two first weeks, while those in HUM# group improved constantly throughout the observation period. Similar trends were observed for the other parameters tested. This study indicates that early global orthogeriatric rehabilitation programs improve the functional performance of elderly patients who sustain hip or humeral fractures. The kinetics of these positive effects differs in the second half of the recovery period depending on the anatomical location of the fracture.

S19

Effets de la menace d'une pandémie de grippe aviaire sur les taux de vaccination de la grippe et du pneumonocoque chez les personnes âgées

Dreher R., Bosshard W., Martin E., Büla Ch. (Gilly, Cully, Epalinges)

But: La menace de pandémie de grippe aviaire a attiré toute l'attention des médias et des recommandations de vaccination contre la grippe spécifiques ont été divulguées. Le but de cette étude est d'évaluer l'effet de ces recommandations sur les taux de vaccination contre la grippe et pneumocoque chez les personnes âgées.
Méthode: les participants (N = 659, âge moyen 81,2 ± 7,4 ans, 69,2% de femmes) sont des personnes âgées hospitalisés dans un service de réadaptation pendant les mois d'hiver entre 1999 et 2007.

Le status fonctionnel, cognitif, l'utilisation de soins à domicile, les données démographiques et le status vaccinal ont été récoltés à l'admission. Les taux de vaccination avant et après les recommandations de menace de grippe aviaire (2006) ont été comparés.
Résultats: Avant l'émission des recommandations contre la grippe aviaire, le taux de vaccination contre la grippe est resté stable entre 1999 et 2005 avec un taux moyen de 64,9% (63,7–66,1%). Après la publication de recommandations spécifiques contre la grippe aviaire le taux de vaccination contre la grippe a augmenté à 73,2% (p = ,07). Une analyse plus approfondie montre que le taux de vaccination a significativement augmenté chez les personnes ne recevant pas d'aide à domicile passant de 57,8% à 73,2% (p = ,02) après publication des recommandations. Chez les personnes recevant de l'aide à domicile il n'y a pas eu d'augmentation du taux de vaccination (71,4 vs 73,1%, p non significatif). Une analyse multivariée restreinte aux personnes ne recevant pas d'aide à domicile, la probabilité d'être vacciné contre la grippe doublait après 2006 (adj OR 1,99; 95% IC 1,08–3,7; p = ,03), ceci indépendamment de l'âge , du sexe et du status fonctionnel et cognitif. Il n'y pas eu d'effet «pandémique» semblable pour le pneumocoque, le taux de vaccination demeurant stable sur toute la période étudiée (6%).
Conclusion: La présence d'une menace de grippe aviaire a clairement augmenté le taux de vaccination contre la grippe chez les personnes âgées. Cet effet a été particulièrement marqué chez les personnes ne bénéficiant d'aucune aide à domicile ce qui suggère une prise de conscience accrue chez les personnes ayant peu de contact avec des professionnels de la santé. Le faible taux de vaccination contre le pneumocoque reste préoccupant.

S20

Does falls efficacy predict gait performance in high-functioning older people?

Rochat S., Martin E., Aminian K., Ganea R., Hoskovec C., Ionescu A., Seematter-Bagnoud L., Najafi B., Piot-Ziegler C., Santos-Eggimann B., Büla C.J. (Lausanne)

Introduction: Falls efficacy, defined as confidence in performing activities without falling, is a measure of fear of falling associated with gait impairment, falls and functional decline in frail older people. This relationship has not been well studied in high-functioning older people.
Objective: To evaluate the relationship between falls efficacy and gait performance in a cohort of high-functioning older people.
Methods: Subjects (N = 864) were a subsample of community-dwelling older people aged 65 to 70 years, enrolled in the "Lc65+" cohort, who completed gait assessment at baseline. Data were collected on demographics, functional, cognitive, affective, and health status. Falls efficacy was assessed using the Falls Efficacy Scale-International (FES-I) that measures confidence in performing 16 activities of daily life (ADL) without falling (score from 16 to 64, higher score indicates lower confidence). Gait parameters were measured over a 20 m walk at preferred gait speed using Physilog, an ambulatory gait monitoring system.
Results: Participants (mean age 68.0 ± 1.4 years, 55.0% women) had excellent physical (92.2% independent in basic ADL, mean gait speed 1.13 ± 0.16 m/sec) and cognitive (98.0% with MMSE ≥24) performance. Nevertheless, 22.1% reported depressive symptoms and 16.1% one or more fall in the previous year. Mean FES-I score was 18.8 ± 4.1. Falls efficacy was associated with gait speed (Spearman rho –0.23, P <.001) and gait variability (Spearman rho 0.10, P = .006), measured by the coefficient of variation of stride velocity. These associations remained in multivariate analysis for both gait speed (adj [beta] coeff: –0.008, 95%CI –0.005 to –0.010, P <.001) and gait variability (adj [beta] coeff 0.024, 95%CI 0.003 to 0.045, P = .023) independent of gender, falls, functional, affective, cognitive, and frailty (Fried's criteria) status. On average, compared to subjects with poor confidence in performing one ADL without falling, those with full confidence had a 0.02 m/sec (2%) faster gait speed and a 2% decrease in gait variability.
Conclusion: Even in high-functioning older people, poor falls efficacy is associated with reduced gait speed and stability, independent of health, functional, and frailty status. The direction of this relationship needs to be investigated prospectively to determine causality and design interventions to improve gait performance, reduce fall risk, and prevent functional decline.

S21

Caractéristiques associées à la vaccination contre la grippe chez les personnes âgées

Bosshard W., Dreher R., Martin E., Büla C.J. (Lausanne)

Objectifs: Décrire les caractéristiques associées à la vaccination contre la grippe dans la population âgée.
Méthodes: Les participants (N = 515) étaient les patients admis en réadaptation durant les hivers 2002–2003 à 2005–2006. Des données socio-démographiques, médicales, fonctionnelles, affectives, cognitives et concernant l'utilisation de soins formels à domicile ont été récoltées. Le statut vaccinal a été déterminé par interview avec le patient.
Résultats: En moyenne, 64.9% des patients (âge moyen 81,3 ± 7,4 ans, 70,1% femmes, 53,0% recevant des soins formels à domicile) rapportaient être vaccinés contre la grippe. Comparés aux autres, les patients vaccinés étaient plus âgés (81,4 ± 7,2 vs 79,9 ± 7,8 ans, P = .007), moins fonctionnels dans les activités de la vie quotidienne de base (5,2 ± 1,1 vs 5,4 ± 0,9, P = ,023), et instrumentales (4,6 ± 2,5 vs 5,3 ± 2,4, P = ,004), et bénéficiaient plus fréquemment de soins formels à domicile (71,4 vs 57,8%, P = ,002). Les patients vaccinés rapportaient plus souvent des symptômes dépressifs (73,0 vs 63,8%, P = ,098), et présentaient moins fréquemment des troubles cognitifs (MMSE <24: 39,8 vs 32,9%, P = ,161), mais ces différences n'étaient pas statistiquement significatives. En analyse multivariée, la vaccination contre la grippe restait associée avec un âge plus avancé (adjOR 1,6, 95%CI 1,1–2,4, P = ,021 pour un âge >80 ans), la présence d'une aide formelle des soins à domicile (adjOR 1,7, 95%CI 1,1–2,5, P = .012), et l'absence de troubles cognitifs (adjOR 1,6, 95%CI 1,0–2,4, P = ,053). Une analyse secondaire révèle que les hommes bénéficiant de soins formels à domicile avaient un taux de vaccination 3 fois supérieur à celui des autres patients (80,7 vs 62,7%, adjOR 3,1, 95%CI 1,2–8,0, P = ,019). Similairement, les patients souffrant de troubles cognitifs étaient un peu plus fréquemment vaccinés s'ils bénéficiaient de soins formels à domicile (69,0 vs 65,0%, adjOR 1,6, 95%CI 0,7–3,8, P = ,329), mais ce résultat n'était pas statistiquement significatif.
Conclusions: La vaccination contre la grippe est plus fréquente chez les patients âgés de plus de 80 ans, ceux sans troubles cognitifs, et ceux bénéficiant de soins formels à domicile, en particulier s'ils sont de sexe masculin. Des stratégies spécifiques ciblant les patients âgés de 65 à 79 ans ne bénéficiant pas de soins formels à domicile devraient être développées pour améliorer les taux de vaccination de ce groupe.

S22

The association between cigarettes smoking, cannabis use and alcohol consumption in a population of young men

Willi C., Cornuz J., Gaume J., Gmel G., Daeppen J.-B. (Lausanne)*

The Association between Cigarettes Smoking, Cannabis Use and Alcohol Consumption in a Population of Young Men.
Background: Some studies suggest that cigarette smoking may have an influence on other risky behaviors but little is known about their chronology of occurrence. The aim of this study was to assess, by young men, what were the other risky behaviors associated with cigarette smoking and the joint prevalence and chronology of occurrence of those risky behaviors.
Method: Cross-sectional analyses of a population-based census of 3526 young men attending the recruitment for the Swiss army, aged between 17 and 25 years old, who filled a self reported questionnaire about their habits. Actual smoking was defined as either regular smoking (≥1 cigarette/day, on every day) or occasional smoking, binge drinking as six or more drinks at least twice a month, at risk drinking as 21 drinks or more per week, and recent cannabis use as cannabis consumption at least once during the last month.
Results: In this population of young men, the prevalence of actual smoking was 51,2%. More than half of the participants (53,8%) had a risky alcohol consumption considered as either binge or at risk drinking, two third (60.1%) ever used cannabis and 25,2% had a recent use of cannabis. In a multivariate logistic regression, odds ratios for smoking were increased for cannabis users (OR 3,10, 95% CI: 2.48–3.88), binge drinkers (OR: 1.77, 95% CI: 1.44–2.17), at risk alcohol drinkers (OR 2.26, 95% CI: 1.52–3.36) and ever users of illicit drugs (OR: 1.56, 95% CI: 1.20–2.03). The majority of young men (57.3%) initiated smoking before cannabis and mean age at onset was 13.4 years old, whereas only 11.1% began to use cannabis before smoking cigarettes and mean age at onset was slightly older (14.4 years old). About a third of participants (30.5%) did have a cluster of risky behaviours (smoking, at risk drinking, cannabis use). More than half of the smokers (59.6%) did cumulate cannabis use and at risk alcohol drinking whereas only 18.5% of non-smokers did.
Conclusions: The majority of young smokers initiated their risky behaviors by first smoking and then by other psychoactive drugs. Smokers had an increased risk to present other risky behaviors such as cannabis use, at risk alcohol consumption and illicit drug use compared to non-smokers. Prevention by young male adults should focus on smoking and also integrate interventions on other risky behaviors.

S23

No healthy heart for heavy drinkers: a population-based study in Switzerland

Foerster M., Marques-Vidal P., Gmel G., Daeppen J.-B., Cornuz J., Hayoz D., Pécoud A., Mooser V., Waeber G., Vollenweider P., Paccaud F., Rodondi N. (Lausanne, Philadelphia)

Background: Low to moderate alcohol consumption has been associated with lower coronary heart disease (CHD) risk, an effect mainly mediated by an increase in HDL-cholesterol levels. However, data on the CHD risk associated with high alcohol consumption are conflicting.
Methods: In a population-based study of 5,769 men and women, aged 35–75 years, without cardiovascular disease in Switzerland, last week alcohol consumption was categorized into 0, 1–6, 7–13, 14–20, 21–27, 28–34, ≥35 drinks/week and into nondrinkers (0 drink/week), moderate (1–13), high (14–34) and very high drinkers (≥35). Blood pressure, lipids and high sensitivity C-reactive protein (hs-CRP) were measured, and the 10-year CHD risk was calculated according to the Framingham risk score.
Results: 73% (n = 4,214) of the participants consumed alcohol; 16% (n = 909) were considered as high drinkers and 2% (n = 119) as very high drinkers. In multivariate analysis, increasing alcohol consumption was associated with higher HDL-cholesterol (from 1.57 ± 0.01 [adjusted mean ± SE] in nondrinkers to 1.88 ± 0.03 mmol/L in very high drinkers); triglycerides (1.17 ± 1.01 to 1.32 ± 1.05 mmol/L), and systolic and diastolic blood pressure rose significantly (127.4 ± 0.4 to 132.2 ± 1.4 and 78.7 ± 0.3 to 81.7 ± 0.9 mm Hg, respectively, all p for trend <0.001). Predicted 10-year CHD risk increased from 4.31 ± 0.10 to 4.90 ± 0.37 (p = 0.03) with increasing alcohol use, with a J-shaped relationship.
Conclusion: As measured by the 10-year CHD risk, the protective effect of alcohol consumption disappears in very high drinkers, namely because the beneficial increase in HDL-cholesterol may be blunt by a rise in blood pressure levels.

S24

Screening undocumented immigrants in Switzerland for tuberculosis and latent tuberculosis infection using the interferon-g assay

Bodenmann P., Vaucher P., Tribolet F., Favrat B., Zellweger J.P. (Lausanne)

Background: Undocumented immigrants are a potential source of tuberculosis (TB) and latent tuberculosis infection (LTBI), but are difficult to screen and treat. In Western Switzerland, there are an estimated 20,000 immigrants/1 million inhabitants, and 90% of them lack medical insurance. Dedicated medical centers for undocumented immigrants facilitate interaction with this population group. In this study, we used the interferon-g assay to assess the prevalence of LTBI in a population of immigrants visiting two urban healthcare centers. We also assessed adherence to preventive or curative treatment, if prescribed.
Methods: All consecutive new patients attending two healthcare centers for undocumented immigrants in Lausanne, Switzerland, between January and July 2007 were offered TB and LTBI screening using a questionnaire on risk factors and current symptoms. The nurse practitioners also offered the interferon-g assay (T-Spot.TB™, Oxford Immunotec). Patients with a positive T-Spot.TB™ or TB symptoms were examined by a physician and had a chest X-ray performed. Adherence to treatment for TB or LTBI was evaluated monthly at visits to the tuberculosis service of the Department of Ambulatory Care and Community Medicine.
Results: Of 161 undocumented immigrants, 131 (81.4%) agreed to be screened; 125 had a complete examination. Of these 125, 51.2% were from South America and 19.2% from Sub-Saharan Africa. Most patients (83.2%) entered Switzerland without passing the official screening procedure for TB for asylum seekers and refugees, and 52% of the patients had been in Switzerland for less than two years. Twenty-four of the 125 patients (19.2%; CI95% 12.7; 27.2) had a positive T-Spot.TB™, and 2/125 had active TB (1.6%; CI95% 0.2; 5.7). Of the 18 patients with LTBI, 4 did not show up for a second visit. Ten patients had an indication for standard isoniazide or rifampicine preventive therapy, but 5 interrupted their treatment before the scheduled end (50% completion rate).
Conclusion: Screening for active and latent tuberculosis in this hard-to-reach population is feasible using dedicated clinics, and the prevalence of TB and LTBI in this population is high. However, the low adherence to treatment for LTBI is an important public health concern, and new strategies are needed to address this.

S25

Prevalence of vitamin B12 deficiency and vitamin B12 depletion: a population based study in a central european country

Risch L., Zerlauth M., Bernasconi L., Saely CH., Risch M., Risch G., Nydegger U. (Liebefeld/Feldkirch, Schaan, Pregassona/Aarau, Feldkirch/Triesen, Liebefeld/Schaan, Liebefeld)

Background: A negative vitamin B12 balance is associated with haematological, neuropsychiatric and cardiovascular symptoms. The condition is diagnosed with laboratory measurement of total vitamin B12 (B12), and, if B12 concentrations are within the grey zone (125–300 pmol/L), more sensitive markers, such as Holotranscobalamin (active B12; aB12). Not much is known about the prevalence of Vitamin B12 deficiency and Vitamin B12 depletion (grey zone B12, aB12 <35 pmol/L) in Central Europe.
Methods: Thus, a cross sectional study was conducted among inhabitants of the principality of Liechtenstein. 7427 consecutive outpatients (mean 48 ± 19 years, range 1–101; 66% female; 19.1% of the country's entire population) undergoing B12 measurement (Beckman Coulter Unicel) for investigation of B12 deficiency were included into the study.
Results: Crude analysis revealed 13.4% of the patients with B12 levels <125 pmol/L indicating B12 deficiency, whereas 74.2% of the patients had B12 within the grey zone. When looking at a subset of patients with aB12 measurement (n = 1328; Abott Axsym), 26.6% had a grey zone B12 together with a low aB12 concentration <35 pmol/L, indicating B12 depletion. Fitting a logistic regression model indicates female gender (p <0.001) and age (p = 0.01) to be significantly associated with B12 deficiency. An interaction term female gender*age (p <0.001) indicates that the association between B12 deficiency & age is stronger among men than among women. The crude period prevalence of B12 deficiency in the entire population amounts at least 2.6% and varies according to age and gender from 0.1–7.1%. Analogously, the period prevalence of patients with B12 depletion can be estimated at 5.1%, varying from 0.2–14.2%.

Conclusions: About 40% of outpatients investigated for B12 deficiency exhibit either B12 deficiency (13.4%) or B12 depletion (26.6%). The respective crude period prevalence among the general population can be estimated at 7.7% (2.6% B12 deficiency/5.1% B12 depletion). Increasing age and female gender are associated with a negative B12 balance.

S26

Sudden death of recreational sportsman myth or reality?

Katz E., Potin M., Kehtari R., Sierro C., Fishman D., Niquille M., Garcia W., Kocher A., Metzger J.-Th. (Lausanne, Neuchâtel, Sion, Genève, Fribourg, Delémont)

Background: Sudden Death (SD) in the athlete is extremly visible phenomenon because of the high profile of professional athletes. Less is known about SD during recreational sport activities. The aim of the present study was to investigate SD among amateur sportsmen in the French-speaking part of Switzerland.
Methods: Data were provided by RRACE cardiac arrest registry which enlisted the help of >1500 general practitioners (GPs), 26 Emergency Medical Services (EMS), 4 alarm centrals and 23 hospitals to consecutively include the data about every adult (>18 years) out-of-hospital SD of non traumatic origin in the French-speaking part Switzerland. (Area covered >12000km^2; adult population 1.5 mln).
Results: After 6 months 14 SD (3% of total amount of out-of-hospital SD) during recreational sport activities were identified, all SD were of cardiac origin. All victims were males, mean age 61.6 years (SD 15.4). Every second victim was known for heart disease (mostly coronary artery disease) and every third suffered from diabetes. Most of victims 10/14 (71%) were jogging or cycling when they suffered from SD. Witnesses were present during 12 events (85%) and every second witness initiated cardio-pulmonary resuscitation (CPR). First recorded rhythm was ventricular fibrillation in 8 victims (57%) and only 2 persons (14%) survived, both in good neurological conditions.
Conclusions: SD during recreational sport activities is not uncommon. Amateur athletes seeking high performance and amateur athletes known for heart disease and diabetes should be strongly advised to enter preparticipational screening programm before starting sporting activities. Since most of sporting activities are practiced in group members of sport societies should be trained to identify cardiac arrest premonitoring symptoms and to initiate CPR.

S27

Depression and anxiety disorders are prevalent in younger patients requesting a check-up exam

Sulger Büel E., Hunziker S., Langewitz W., Nüesch R., Battegay E., Zimmerli L. (Basel, Zürich)

Objective: Patients who request a general check-up are often motivated by specific symptoms and health concerns and rarely seek out physicians for preventive issues. Furthermore, anxiety and mood disorders may prompt patients to ask for a check-up exam. We hypothesized that psychiatric disorders are more prevalent in "check-up" patients compared to patients who schedule an appointment for other reasons than a check-up exam.
Design and method: We screened 66 patients who requested a check-up exam (43 men and 23 women, mean age 45±16 years) and 100 patients who scheduled an appointment for other reasons than "check-up" (61 men and 39 women, mean age 45 ± 17 years) for anxiety disorders and depression. Three validated easy-to-administer tools to screen for psychiatric disorders such as anxiety disorders and depression were used: the PRIME-MD, Hospital Anxiety and Depression Scale, and Brief Symptom Inventory. All patients were asked to fill out the questionnaires before their first medical consultation at the Outpatient Department of the University Hospital Basel.
Results: The prevalence of anxiety disorder or depression using these screening questionnaires was similar between check-up and control patients (29% vs. 41%, p = 0.11). In control patients there was no difference in prevalence of anxiety disorder or depression between younger and older individuals. However, in check-up patients psychiatric disorders were more prevalent in patients younger than 40 years of age (p = 0.02 for depression and anxiety disorder, respectively): in this age group, screening tools were positive for anxiety disorders in 31% and depression in 41% of patients.
Conclusions: Psychiatric comorbidities are frequent in a general internal medicine outpatient setting. There is no difference in prevalence between check-up patients and patients who schedule an appointment for reasons other than check-up. However, younger patients who request a check-up exam demonstrate increased psychiatric comorbidity.

S28

Diagnosing pulmonary embolism by multi-detector computed tomography alone or combined with lower limb venous ultrasonography: a randomized non-inferiority trial

*Righini*M., Le Gal G., Aujesky D., Roy P-M., Sanchez O., Verschuren F., Rutschmann O., Nonent M., Cornuz J., Thys F., Petit Le Manach C., Revel M.-P., Poletti P.-A., Meyer G., Mottier D., Perneger T., Bounameaux H., Perrier A. (Genève, Brest, Lausanne, Angers, Paris, Bruxelles, Genève Md)*

Background: Recent data suggest that multi-slice computed tomography (MSCT) combined with D-dimer measurement may safely rule out pulmonary embolism. We compared this combination with a strategy in which both a negative lower limb vein ultrasonography and a negative MSCT were required to rule out pulmonary embolism.
Methods: We included 1819 consecutive outpatients with clinically suspected pulmonary embolism in a multicentre non-inferiority randomized controlled trial comparing two strategies: clinical probability assessment and either 1) D-Dimer measurement and computed tomography (DD-CT strategy) or 2) D-Dimer measurement, lower limb vein compression ultrasonography and computed tomography (DD-US-CT strategy). The main outcome was the 3-month thromboembolic risk in patients left untreated based on the exclusion of pulmonary embolism by the diagnostic strategy.
Findings: The prevalence of PE was 21% in both study arms. In the per-protocol analysis, the 3-month thromboembolic risk was 0.3% (95% CI: 0.1–1.1) in the DD-US-CT arm and 0.3% (95% CI: 0.1–1.2) in the DD-CT arm, a non-significant difference (0.0; 95% CI: –0.9 to 0.8). Results were similar in the intention-to-diagnose analysis. In the DD-US-CT arm, ultrasonography showed a deep venous thrombosis, hence allowing foregoing MSCT, in 9% of patients. The mean cost per patient was 20 to 30% higher in the DD-US-CT strategy.
Interpretation: The strategy combining D-Dimer and MSCT is as safe as the strategy combining D-dimer, MSCT and lower limb vein compression ultrasonography for excluding pulmonary embolism. Although the diagnostic yield of ultrasound is low when performed before MSCT, it may remain of interest in patients with a contraindication to CT.

S29

A simple score for estimating ischemic heart disease in patients with non-traumatic chest pain in primary care

Gencer B., Herzig L., Verdon F., Vaucher P., Burnand B., Bischoff T., Mühlemann N., Favrat B. (Lausanne, Epalinges, Neuchâtel, Bex)

Background: Modelling epidemiological knowledge in validated clinical scores is a practical mean of integrating EBM to usual care. Existing scores about cardiovascular disease have been largely developed in emergency settings, but few in primary care. Such a toll is needed for general practitioners (GP) to evaluate the probability of ischemic heart disease (IHD) in patients with non-traumatic chest pain.
Objective: To develop a predictive model to use as a clinical score for detecting IHD in patients with non-traumatic chest-pain in primary care.
Methods: A post-hoc secondary analysis on data from an observational study including 672 patients with chest pain of which 85 had IHD diagnosed by their GP during the year following their inclusion. Best subset method was used to select 8 predictive variables from univariate analysis and fitted in a multivariate logistic regression model to define the score. Reliability of the model was assessed using split-group method.
Results: Significant predictors were: age (0–3 points), gender (1 point), having at least one cardiovascular risks factor (hypertension, dyslipidemia, diabetes, smoking, family history of CVD; 3 points), personal history of cardiovascular disease (1 point), duration of chest pain from 1 to 60 minutes (2 points), substernal chest pain (1 point), pain increasing with exertion (1 point) and absence of tenderness at palpation (1 point). Area under the ROC curve for the score was of 0.95 (IC95% 0.93; 0.97). Patients were categorised in three groups, low risk of IHD (score under 6; n = 360), moderate risk of IHD (score from 6 to 8; n = 187) and high risk of IHD (score from 9–13; n = 125). Prevalence of IHD in each group was respectively of 0%, 6.7%, 58.5%. Reliability of the model seems satisfactory as the model developed from the derivation set predicted perfectly (p = 0.948) the number of patients in each group in the validation set.
Conclusion: This clinical score based only on history and physical exams can be an important tool in the practice of the general physician for the prediction of ischemic heart disease in patients complaining of chest pain. The score below 6 points (in more than half of our population) can avoid demanding complementary exams for selected patients (ECG, laboratory tests) because of the very low risk of IHD. Score above 6 points needs investigation to detect or rule out IHD. Further external validation is required in ambulatory settings.

S30

Prevalence of reduced estimated Glomerular Filtration Rate (eGFR) in the anemic elderly

Risch L., Saely Ch., Gouya G., Hoefle G., Kiss D., Zerlauth M., Risch G., Nydegger U., Drexel H., Risch M. (Liebefeld, Feldkirch, Liestal, Schaan)

The clinical importance to identify even mild chronic kidney disease (CKD) in older people is centered on prevention of progression to endstage renal failure, anemia, renal osteopathy and to cardiovascular disease. Whereas decreased production of erythropoietin in chronic kidney disease (CKD) is well known as a potential cause of anemia, the contribution of CKD to anemia has not yet fully been defined on a public health basis. We therefore investigated a representative homogenous patient group (N = 8.410, 38% of Liechtenstein's entire population) seeking clinical attention for non-nephrological care. This group was screened for anemia (WHO criteria employing haemoglobin cutoffs m/f <130/120 g/L). In addition, renal function was assessed by means of the abbreviated MDRD equation. Creatinine was measured by an alkaline picrate method revealing concentrations traceable to the reference method IDMS (Cobas Integra, Roche Diagnostics, Rotkreuz). Anemia was present in 15.7% (n = 1324) of the patients. An eGFR <60 ml/min/1.73 m^2 was found in 8.8%. Twenty-seven percent of the patients with anemia had an eGFR <60 ml/min/1.73 m^2. In crude analysis, there was a strong association between the presence of anemia and an eGFR <60 ml/min/1.73 m^2 (OR 6.5, 95% CI 5.56, 7.65). In a logistic regression model, age (OR 1.036, 96%CI 1.032, 1.040/year), female gender (OR 1.33, 05% CI 1.17, 1.52) and an eGFR <60 ml/min/1.73 m^2 significantly predicted presence of anemia, the latter criterion being the strongest predictor (OR 3.025I, 95% 2.53, 3.61). An interaction term age*GFR category reached significance (p <0.001), pointing to an association between impaired renal function and anemia which was significantly stonger among elderly compared to younger patients. It is concluded that a reduced eGFR <60 ml/min/1.73 m^2 is a prevalent circumstance in patients with anemia. Moreover, such prevalence increases with age, reaching about 50% in patients aged >80 yrs. It may be concluded, that recognition of anemia imperatively should prompt evaluation for kidney function, especially in elderly patients.

S31

Accuracy of diagnosis and awareness of cardiovascular risk factors and metabolic syndrome in doctors and patients

Gschwend S., Stöckli R., Schöbi N., Nüesch R., Battegay E., Zimmerli L. (Basel, Zürich)

Objective: The metabolic syndrome (MS), a clustering of several commonly occurring abnormalities that include abdominal obesity, hypertriglyceridemia, low high-density lipoprotein level, hypertension, and hyperglycemia has gained attention due to its impact on cardiovascular diseases and its increasing prevalence. Adequate awareness of MS is a key first step that enables patients to address their risk factors (RF). We hypothesized that patients are inadequately informed about their own RF, and that their treating physicians underdiagnose the presence of the MS.
Design and method: We prospectively examined a total of 415 consecutive patients (210 women and 205 men, mean age 46 ± 17 years, range 16–86 years) during their first medical consultation at the Outpatient Department of the University Hospital Basel. Based on the physical exam and the patient's history treating physicians had to judge whether MS might be present or not. After the consultation the components defining MS were measured in all patients. The ATP III-definition of MS was used. Patients were asked to recall as many cardiac RF as possible.
Results: The observed prevalence of MS was 18% (32/210 women and 41/205 men). The probability of MS was 57% [95% CI 48–66], given a positive judgement by the physician (positive predictive value), and the probability of absence was 92% [95% CI 90–94], given a negative judgement (negative predictive value). In patients, mean RF knowledge was 2.5 ± 1.4 (median 3) out of a possible 12. Smoking (64%), physical inactivity (49%) and obesity (43%) were the RF most commonly reported whereas lipid abnormalities (22%), hypertension (21%) and diabetes (12%) were mentioned by a minority of patients. Patients affected by RF did not recall them more often than patients without the corresponding RF.
Conclusions: Physicians' judgment of MS based on physical exam and patient's history is accurate, i.e. only few cases are missed (good NPV). However, to increase PPV laboratory findings should be incorporated in the judgement. Patients have limited knowledge about cardiovascular RF, whether affected by them or not.

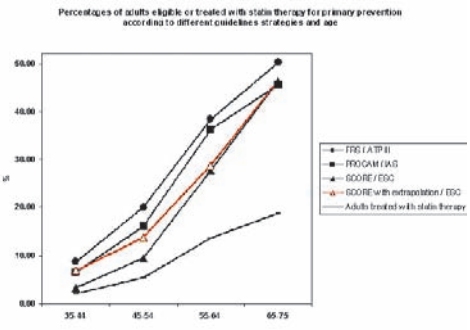
S32

Eligibility for statin therapy in primary prevention: discrepancies using different guidelines in a population-based study in Switzerland

Nanchen D., Chiolero A., Cornuz J., Firmann M., Marques-Vidal P., Mooser V., Paccaud F., Waeber G., Vollenweider P., Rodondi N. (Lausanne, Collegeville)

Introduction: Recommendations for statin use for primary prevention of coronary heart disease (CHD) are based on estimation of the 10-year CHD risk. We compared the 10-year CHD risk assessments and eligibility percentages for statin therapy using three scoring algorithms currently used in Switzerland.
Methods: We studied 5683 women and men, aged 35–75, without overt cardiovascular disease (CVD), in a population-based study in Lausanne, Switzerland. We compared the 10-year CHD risk using three scoring schemes, i.e., the Framingham risk score (FRS) from the U.S. National Cholesterol Education Program's Adult Treatment Panel III (ATP III), the PROCAM scoring scheme from the International Atherosclerosis Society (IAS), and the European risk SCORE for low-risk countries, without and with extrapolation to 60 years as recommended by the European Society of Cardiology guidelines (ESC). With FRS and PROCAM, high-risk was defined as a 10-year risk of fatal or non-fatal CHD >20% and a 10-year risk of fatal CVD >= 5% with SCORE. We compared the proportions of high-risk participants and eligibility for statin use according to these three schemes. For each guideline, we estimated the impact of increased statin use from current partial compliance to full compliance on potential CHD deaths averted over 10 years, using a success proportion of 27% for statins.
Results: Participants classified at high-risk (both genders) were 5.8% according to FRS and 3.0% to the PROCAM, whereas the European risk SCORE classified 12.5% at high-risk (15.4% with extrapolation to 60 years). For the primary prevention of CHD, 18.5% of participants were eligible for statin therapy using ATP III, 16.6% using IAS, and 10.3% using ESC (13.0% with extrapolation) because ESC guidelines recommend statin therapy only in high-risk subjects. In comparison with IAS, agreement to identify eligible adults for statins was good with ATP III, but moderate with ESC (Figure). Using a population perspective, a full compliance with ATP III guidelines would reduce up to 17.9% of the 24'310 CHD deaths expected over 10 years in Switzerland, 17.3% with IAS and 10.8% with ESC (11.5% with extrapolation).
Conclusion: Full compliance with guidelines for statin therapy would result in substantial health benefits, but proportions of high-risk adults and eligible adults for statin use varied substantially depending on the scoring systems and corresponding guidelines used for estimating CHD risk in Switzerland.

Figure



S33

Cost-effectiveness and cost-utility of risedronate for osteoporosis treatment and fracture prevention in women: a swiss perspective

Wasserfallen J-B., Krieg M-A., Greiner R-A., Lamy O. (Lausanne, Lörrach)

Introduction: Risedronate has been shown to reduce the risk of fractures in postmenopausal osteoporotic women. We assessed its cost-effectiveness and cost-utility along different risk profiles using computer modelling.
Methods: A previously validated Markov model was used and populated with mortality, fracture incidence and cost data specific to Switzerland, as well as published utility values, and run on a population of 1000 women of 70 years with previous vertebral fracture, treated over 5 years with risedronate 35 mg weekly (base case). Another 119 scenarios were investigated in 5 cohorts (according to age at the start of therapy) with 8 risk factor distributions and 3 lengths of residual effects after end of risedronate administration. Sensitivity analyses included the effect of input parameter variation on key outcomes. The outcomes were cost per hip fracture averted, cost per any fracture averted and cost per quality-adjusted life year (QALY) gained.
Results: Risedronate therapy proved to be the dominant strategy in base case population. In the presence of a previous vertebral fracture risedronate was dominating in all scenarios from age 65 and even at age 60 when assuming a 5 year residual effect. For all osteoporotic women >60 years of age with at least one risk factor, cost-utility ratio ranged from below CHF 50,000 to cost-saving. Age at start of therapy and fracture risk profile had a significant impact on results. Sensitivity analysis did not markedly change the results.
Conclusions: Assuming a 2 year residual effect, cost-utility ratio of risedronate in women with postmenopausal osteoporosis is below accepted thresholds from age 60 and even cost saving above the age of 65 for all risk scenarios.

S34

Molecular and cellular effects of dietary alpha-linolenic acid on atherogenesis and membrane lipid profiles

Matter C.M., Scheeder M.R., Lohmann C., Lüscher T.F., Beer J.H. (Uni Zürich, ETH Zürich, KS Baden)

Background: The beneficial effects of long-chain n-3 fatty acids (LC-n-3 FA) of marine origin on lipids, cardiac arrhythmia and cardiovascular events are well documented. However, the relevance of plant-derived C18:3n3 FA (alpha-linolenic acid, ALA) remains uncertain. Furthermore, the capacity for chain elongation is thought to be very limited in mammals. We have recently reported on increased concentrations of ALA in alpine cheese and on its potential benefits ("The alpine paradox").
Aims: We tested the hypothesis that a) an ALA-rich diet reduces atherosclerosis and b) a conversion of ALA into LC-n-3 FA can be detected in the membrane FA profile.
Methods and results: Eight weeks old male ApoE-/- mice were fed a standardized, 0.15% cholesterol diet for 16 weeks containing either a high ALA (HI, 7g%; n = 14) or standard low ALA diet, (LO, 0.03%; n = 12). ALA was offered as flaxseed oil, while the control was compensated with cocoa butter. Plaque area in the aortic arch, as quantified by oil-red O staining was significantly reduced (119,009 um^2 vs. 69,026 um^2; p = 0.006). T cell content (CD3 positivity) was also significantly decreased (902 um^2 vs. 128 um^2; p = 0.004) The macrophage content (CD68 positivity) was non-significantly reduced. Weight gain was similar in both groups. The conversion of ALA into LC-n-3 FA was analyzed by gas chromatography and is given as the FA percentage in red cell membranes (Table). The data indicate an increased membrane incorporation of ALA, a 7x shift in the n6/n3 ratio and a 5x shift in the LC-n-3 FA content (EPA, DPA and DHA). On the other hand, arachidonic acid (ARA) content was only 1/5 of the LO-population.
Conclusions: A diet rich in ALA reduces atherosclerosis and T cell infiltration in ApoE-/- mice. It induces an important chain elongation into LC-n-3 FA resulting in a favourable FA profile. Given the limited fishery resources, ALA may represent a (cost)-effective and attractive nutritional supplement.

Table 1

	HI	LO
n6 Total (g%)	18.9 ± 0.9	27.6 ± 0.8
n3 Total	15.5 ± 1.2	3.1 ± 0.1
n6/n3-Ratio	1.2 ± 0.1	8.9 ± 0.6
ARA/EPA-Ratio	0.2 ± 0.01	189 ± 39
C18:3n-3 (ALA)	2.24 ± 0.32	0.07 ± 0.06
C20:3n-3	0.3 ± 0.04	0.09 ± 0.03
C20:5n-3 (EPA)	4.39 ± 0.3	0.08 ± 0.05
C22:5n-3 (DPA)	4.1 ± 0.30	0.31 ± 0.02
C22:6n-3 (DHA)	4.06 ± 0.6	2.56 ± 0.15
C20:4n-6 (ARA)	2.94 ± 0.25	14.3 ± 0.58

S35

Akutes Nierenversagen – ist die intermittierende Hämodialyse bei schwer kranken Patienten noch gerechtfertigt?

Rupprecht C., Bleisch J., Ursprung T., Stäubli M., Franzen D. (Zollikerberg)

Hintergrund: Das akute dialysepflichtige Nierenversagen ist mit einer hohen Mortalität von 35–80% assoziiert. Bei der Behandlung stehen zwei Nierenersatzverfahren zu Verfügung: kontinuierliche Hämo(dia)filtration und intermittierende Hämodialyse (IHD). Die Überlegenheit eines der beiden Verfahren wird in Bezug auf die Mortalität und die Nierenerholungsrate kontrovers diskutiert. Im Rahmen eines Multiorganversagens (MODS) wird jedoch das kontinuierliche Verfahren bevorzugt, mit der Begründung, dass gehäuft arterielle Hypotonien während der IHD auftreten. Ist die IHD bei schwer kranken Patienten mit MODS noch gerechtfertigt?
Methoden: Im Zeitraum von 6 Jahren wurden 53 Patienten (Durchschnittsalter 68 Jahre) retrospektiv analysiert, welche aufgrund eines akuten Nierenversagens auf der Intensivstation einer IHD unterzogen wurden. In 53% trat das Nierenversagen im Rahmen eines MODS auf. Der durchschnittliche APACHE II Score betrug 20. Häufigste Ursache war eine Tubulusnekrose (85%). Die IHD wurde in der Regel täglich (77%) mit einer durchschnittlichen Ultrafiltrationsrate von 507 ml/h durchgeführt.
Resultate: Die Mortalität betrug 30,2%. Signifikante Risikofaktoren stellen ein MODS (p = 0,001), metabolische Azidose (p = 0,0001), mechanische Beatmung (p = 0,003) und arterielle Hypotonie (p = 0,0001) dar. Zu Komplikationen kam es in 32%, wobei die arterielle Hypotonie am häufigsten war (24%). Risikofaktoren für hämodynamische Zwischenfälle während der IHD waren ein MODS (p = 0,009), ARDS und Beatmungspflicht (p = 0,015 bzw. 0,003), hohe Ultrafiltrationsraten (p = 0,032) sowie die tägliche (im Vergleich zur alternierenden) Hämodialysefrequenz (p = 0.002).
Schlussfolgerung: Auch bei Patienten mit MODS und/oder arterieller Hypotonie kann die IHD zur Behandlung des akuten Nierenversagens durchaus empfohlen werden. Denn trotz hohem Anteil an Patienten mit MODS ist die Mortalität im vorliegenden Krankengut im Vergleich zur Literatur tief. Somit kann davon ausgegangen werden, dass die Auswahl des Nierenersatzverfahrens in Bezug auf die Mortalität nicht massgebend ist. Vielmehr sind die genannten Risikofaktoren (MODS, metabolische Azidose, respiratorische Insuffizienz und arterielle Hypotonie) für die Prognose entscheidend. Diese gilt es früh zu erfassen und zu therapieren. In diesem Zusammenhang sind geringere Ultrafiltrationsraten mit kompensatorisch verlängerter Hämodialysedauer zu empfehlen.

S36

Congruence between referring and hospital physicians about the reasons for admission in a supportive care unit – comparison with cancer patients' evaluation of their main symptoms

Luthy C., Cedraschi C., Chouiter A., Konrad-Mugnier B., Rapiti E., Allaz A.F. (Geneva)

Background: Patients admitted in a supportive care unit often present with intricate somatic and psychosocial problems. In this context, congruence between referring and hospital physicians on how they prioritize symptoms and treatments raises important issues. Whether these priorities correspond to the patients' views remains an open question.
Objective: To assess the level of congruence between referring and hospital physicians regarding the identified reasons for admission of patients hospitalized in a supportive care unit, and to compare these reasons with the main symptoms patients identify.
Methods: Data concerning 83 consecutive patients were collected by means of a structured questionnaire: the reasons for admission according to the referring physician and to the physician in charge of the hospital unit were assessed in nine categories not mutually exclusive. Patients were asked to complete a questionnaire evaluating their main symptoms at the time of admission. Socio-demographic and clinical characteristics of the patients were also recorded. Kappa statistics were used to compare the agreement between physicians; and between the physicians and the patient.
Results: 67% of the patients were men; mean age was 65 years (SD = 14). A wide range of cancer diagnoses were represented; 23% had primary local diseases, 42% had local recurrences, and 35% had metastatic diseases. Median time since diagnosis was 1.8 years (range = 0.1–12.5 years). Identified main reasons for admission were similar in both groups of physicians and Kappa values indicated a fair (K between 0.4 and 0.7) to good (K >0.7) congruence. Asthenia was the most frequently mentioned reason (33% in referring physicians vs 55% in physicians in charge, K = .49), followed by functional problems (30% vs 53%, K = .48), pain (37% vs 49%, K = .71), nutrition (19% vs 38%, K = .47), dyspnoea (17% vs 20%, K = .78). Complications of oncological treatment, psychosocial difficulties, and behavioural problems were less frequently mentioned. Fatigue was also the main symptom reported by the patients, although with a much higher prevalence (85%), followed by pain (44%), nutrition (40%), anxiety (38%), and dyspnoea (35%). Congruence between patients' evaluation and physicians was poor (K <0.4).
Conclusions: The level of congruence between referring and hospital physicians regarding the reasons for admission of patients hospitalized in a supportive care unit was satisfactory. This is important in terms of coordinated care between ambulatory and hospital settings and may contribute to continuity of care. However, patients' reports put a different emphasis on the symptoms they experience thus illustrating the challenges of shared goal-setting.

S37

Perceptions and use of communication skills in outpatient and inpatient settings: implications for training

Junod Perron N., Sommer J., Hudelson P., Demaurex F., Luthy C., Nendaz M., Dolmans D., Van der Vleuten C., de Grave W. (Geneva, Maastricht)

Background: Understanding how the working setting influences physicians' perception and use of communication skills is important for designing effective training programmes in this field.
Objectives: to explore how physicians perceive and use communication skills in in-patient and out-patient settings.
Methods: A self-administered questionnaire and 4 focus groups were conducted with residents and clinical supervisors in two inpatient services and one outpatient clinic of the Geneva University Hospitals. Descriptive statistics were used for the questionnaire. Focus groups were audio taped, transcribed verbatim and analyzed in a thematic way using Winmax software for qualitative data analysis.
Results: Outpatient physicians tended to be older, more trained in and more receptive to communication skills. These physicians reported that communication skills were especially useful in addressing chronic diseases and patients' social problems, and thought that the use of good communication skills could be therapeutic for the patient. In contrast, inpatient physicians valued communication skills because they contributed to their own well-being and helped them keep control of the situation. In particular, they emphasized the importance of good communication skills for dealing with family conflicts, end of life issues and patients with substance-abuse problems. The areas in which physicians desired more training reflected their perceptions of the utility of communication skills: inpatient physicians wanted more training in how to break bad news, manage conflicts and inform patients while outpatient physicians gave priority to listening skills, showing empathy, exploring patients' perspectives and structuring the consultation.
Conclusion: Differences in service priorities and demands, as well as physicians' professional development process must be taken into consideration when developing a training program in communication skills.

S38

Psychosocial vulnerability in fibromyalgia patients: a role for COMT polymorphism?

Desmeules J., Piguet V., Besson M., Chabert J., Rapiti E., Rebsamen M., Rossier M., Dayer P., Cedraschi C. (Genève)

Introduction: Fibromyalgia (FM) is a chronic musculoskeletal syndrome, and patients experience functional impairments, emotional distress and a negative quality of life. The frequent polymorphism Val158Met of the gene encoding catechol-O-methyltransferase (COMT) is associated with a reduction in the enzyme activity that influences pain regulation and anxiety and may participate in chronic painful diseases. We investigated the influence of COMT polymorphism on psychosocial variables in FM patients and healthy controls.
Methods: 198 patients underwent a quantitative sensory testing requiring 2 weeks medication withdrawal; 137 were classified as able to stop medication (ASM) and 61 were classified as unable to stop medication (USM); 99 healthy controls were included. Psychosocial aspects were investigated by means of questionnaires investigating health related quality of life, physical activities, and mood (Fibromyalgia Impact Questionnaire, Psychological General Well-Being, SF-36, State-Trait Anxiety Inventory, Beck Depression Inventory, and Catastrophizing Scale). Assessment of the control group included the same questionnaires, except FIQ. The COMT Val158Met polymorphism was assessed by TaqMan PCR.
Results: Most subjects were middle-aged females, with a 10 year mean duration of symptoms. Over half were either on sick-leave or on disability pension. Clinical measures indicated moderate to severe pain in both groups of FM; 49% of the ASM group was on antidepressant medication prior to the entry in the study and nearly all the USM (92%) were using antidepressants (p <0.001). The measures of psychosocial and functional aspects showed severe impairments in FM patients as compared to controls (p <0.05, for all scales) and indicated that the USM patients suffered more severe functional, cognitive and emotional limitations than ASM. The distribution of the COMT polymorphism was similar in controls and in FM patients. However, when considering FM subgroups, the Met/Met genotype was clearly over-represented in USM patients (36% vs 19% in ASM and 25% in controls; p <0.05). Analysis of ASM patients with a Met/Met genotype showed systematically worse scores on all psychosocial variables.
Conclusion: These results suggest a role of the COMT Val158Met polymorphism in the increased psychosocial vulnerability (i.e. anxiety, catastrophizing, depression) observed in FM patients. This may be of importance as identifying patient subgroups is a major challenge in the treatment of FM.
Supported by the SNSF (NRP53–4049-405340-104645/1)

S39

Assessment of doctors' medical and cultural competence using virtual patients

Junod Perron N., Perneger T., Kolly V., Hudelson P. (Genève)

Background: As patient populations become increasingly diverse, physicians need not only to master biomedical aspects of care, but also to be sensitive to the ways in which culture and language can influence clinical communication and care. The goal of our study was to examine physicians' use of appropriate biomedical and cultural skills during clinical encounters with migrant patients, and the relationship between the two skill sets.
Methods: We developed two detailed patient "stories" or scenarios and incorporated them into an interactive, computer-based program (VIPS) designed to test clinical skills. Participants (doctors and medical students in their clinical years) could ask any number of questions to arrive at their diagnosis. For each scenario, we constructed two scores to assess whether physicians asked questions that were appropriate from a biomedical and from a cultural standpoint. These scores were based on an a priori determination of appropriateness of each question.
Results: Each virtual patient was assessed by 111 and 99 participants; 92 participants assessed both. The participants asked on average 8.4 (SD 2.6) and 7.9 (SD 3.5) medically indicated questions and 1.4 (SD 1.0) and 2.3 (SD 1.4) culturally appropriate questions. Correlations of the medical scores (r = 0.49, p <0.001) and of the cultural scores (r = 0.46, p <0.001) were moderate but statistically significant. Within each virtual patient, the medical and cultural scores were less correlated (r = 0.26 and 0.39, both p <0.005). No respondent characteristics were consistently associated with higher or lower scores.
Conclusions: The VIPS program appears to be reliable. However, we found only a modest correlation between physicians' use of appropriate biomedical and cultural skills, and scores were not associated with years of experience. These results raise several questions regarding the operationalization of biomedical and cultural skills in this study and the relationship between the two skill sets.

S40

Clonal analysis of deletions on chromosome 20q and JAK2-V617F in MPD suggests that del20q acts independently and is not one of the pre-disposing mutations for JAK2-V617F

Schaub F., Looser R., Tiedt R., Hermouet S., Kralovics R., Girodon F., Tichelli A., Skoda RC. (Basel, Nantes, Wien, Dijon)

Deletions on the long arm of chromosome 20 (del20q) are the most common chromosomal aberration in myeloproliferative disorders (MPD) and can be found in the bone marrow from 0.2% of patients with essential thrombocythemia (ET), 8% of polycythemia vera (PV) and 7% of primary myelofibrosis (PMF). The common deleted region has been mapped, but no gene mutations have been detected to date. The del20q and JAK2-V617F can occur simultaneously in the same patients. We previously described two such patients and found that the size of the del20q clone by far exceeded the size of the clone carrying JAK2-V617F, suggesting that del20q preceded the acquisition of the JAK2-V617F mutation. To address the role of del20q and JAK2V617F mutations in the pathogenesis of MPD, we studied their temporal order of occurrence using clonogenic assays. We screened DNA from granulocytes of 666 MPD patients (263 PV, 320 ET, 83 PMF) for the presence of del20q using a quantitative gene copy number PCR assay with primers placed in two different exons of *L3MBTL*, a gene located in the common deleted region. Since this assay is positive only if the majority of granulocytes have lost a copy of *L3MBTL*, this method selects for del20q events that dominate in the peripheral blood. Del20q was found in a total of 19/666 MPD patients (2.9%) and 17 of these 19 patients were also positive for JAK2-V617F. The frequency of del20q was 3/320 (0.9%) in ET, 7/263 (2.7%) in PV, and 9/83 (11%) in PMF. Samples that showed a decrease in copy number in the initial screen were validated using primers in neighbouring genes or comparative genomic hybridization using high-density oligonucleatide arrays. We performed colony assays in methylcellulose with peripheral blood from 5 patients positive for del20q, of which 4 were also positive for JAK2-V617F. To determine the clonal distribution, single BFU-E colonies grown in the presence of erythropoietin were picked and analyzed individually for the presence of del20q and/or JAK2-V617F. We found that in 2 patients del20q occurred before JAK2-V617F, whereas in 2 other cases del20q was acquired after the acquisition of JAK2-V617F. The lack of a consistent temporal pattern of occurrence of del20q in respect to JAK2-V617F suggests that del20q acts independently and is not one of the pre-disposing mutations for JAK2-V617F.

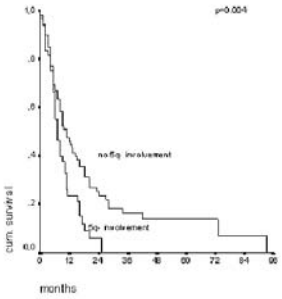
S41

Dependency of survival on additional karyotype anomalies and bone marrow blast count in patients suffering from myelodysplastic syndromes with 5q deletion

Blum S., Hildebrandt B., Jotterand M., Schapira M., Giagounidis A., Aul C., Germing U. (Lausanne, Düsseldorf, Duisburg)

The 5q deletion syndrome is described as having a favourable outcome in MDS. Little data is available concerning del(5q) and additional karyotype anomalies or bone marrow blast count. We screened the our MDS registries to obtain data on patients with karyotype anomalies including del(5q). 1073 patients were karyotyped at diagnosis. 198 patients with del(5q) with or without other karyotype anomalies and 105 patients with complex karyotype without del(5q) were analysed. 106 patients showed del(5q) as single anomaly, 23 had 1 additional anomaly, 69 had 2 or more additional anomalies and were classified as complex karyotype. In del(5q) only, mean survival was 76 months as compared to 42 months in normal karyotype. In the group with 1 additional anomaly mean survival was 47 months ($p = 0.02$), in the group with 2 or more additional anomalies 7 months ($p = 0.0005$). Survival differed significantly in each subgroup for patients with more or less than10% of bone marrow blasts. Patients with del(5q) only show a median survival of 12 months when presenting with more than 10% medullary blasts. Patients with a complex karyotype including del(5q) with less than 5% medullary blasts had a median survival of 12 months, but median survival was only 6 months in patients with elevated medullary blasts. By multivariate analyses, we found that additional karyotype anomalies, followed by an elevated medullary blast count above 10% are the most important independent prognostic parameters. We compared the group del(5q) and 2 or more additional anomalies (n = 69) to patients with complex karyotype anomalies not including del(5q) (n = 105). Median survival of the group including del(5q) was 7 months as compared to 12 months in the group without del(5q) ($p = 0.02$). 12 months after diagnosis, 30% of the group with del(5q) in a complex karyotype was alive as compared to 45% of the group with a complex karyotype without del(5q). Disease related death was noted in 77% of patients with a complex karyotype and del(5q) and 73% without del(5q). Our data show that survival in patients with del(5q) is dependent on the number of additional karyotype anomalies as well as medullary blast count. The prognosis of MDS with del(5q) is associated with an extremely poor prognosis when diagnosed within a complex karyotype. Although there are no substantial differences in clinical, haematological and morphological data between patients with or without del(5q), the median survival differs significantly.

Figure 1: KM Plots presenting survival of patients with a complex karyotype with or without inclusion of del(5q)



S42

Junctional adhesion molecule C (JAM-C) constitutes a new diagnostic marker for B cell lymphoproliferative syndromes

Matthes T., Ody C., Jungblut-Ruault S., Cossali D., Barnet M., Aurrands-Lions M., Imhof BA. (Genève, Marseille)

Differentiation of naïve B cells into plasma cells or memory cells occurs in the germinal centers (GC) of lymph follicles or alternatively via a GC- and T cell independent pathway. It is currently assumed that B cell lymphomas correlate to normal B cell differentiation stages, but the precise correlation of several B cell lymphomas to these two pathways remains controversial. We recently described the junctional adhesion molecule C (JAM-C), a molecule originally identified at the cell-cell border of endothelial cells, as a new B cell marker with a tightly regulated expression during B cell differentiation: immature CD10+ B cell in the bone marrow do not express JAM-C; naïve, mature, peripheral blood B cells express it weakly; CD27+ memory B cells strongly; and bone marrow plasma cells are again JAM-C negative (Leukemia; 2007 Jun; 21(6):1285–93). Of particular interest, JAM-C expression divides CD27+ tonsillar B cells into two subpopulations: JAM-Cneg cells, with a phenotype of germinal center B cells and a high expression of BCL-6, a nuclear proto-oncogene with a pivotal role in GC-formation, and JAM-Cpos cells, corresponding to non-germinal B cells, derived partly from the marginal zone. In vitro cultures of the different tonsillar B cell subpopulations (CD27+JAM-C+, CD27+JAM-Cneg, CD27negJAM-C+) confirmed these results, since Ig-secretion measured after 7 days of culture, was minimal in naïve CD27neg cells, CD27+Jam-C GC cells produced mainly IgG, and non-GC JAM-C+CD27+ B cells mainly IgM. Simultaneous analysis of JAM-C and CD27 expression in peripheral blood lymphocytes (PBLs) from a series of 86 patients with various lymphoproliferative syndromes (LPSs) allowed a clear classification into two types of B cell malignancies: JAM-Cneg lymphomas (CLL, follicular lymphoma, DLBL, multiple myeloma, and B-ALL), and JAM-C expressing lymphomas (mantle cell lymphoma, marginal zone B cell lymphoma, hairy cell leukemia). In 13 LPSs a clear diagnosis could not be obtained using classical surface markers, immunohistology, and cytogenetic analyses, in particular in cases on the borderline between MCL, CLL and MZBL. The use of JAM-C in the diagnostic work-up of these cases will be discussed. In conclusion, we suggest that JAM-C constitutes a new diagnostic marker for the characterisation of lymphoproliferative B cell syndromes, and in particular for the positive diagnosis of lymphomas derived from the marginal zone.

S43

**Significantly Shorter Telomeres in T-Cells of ZAP-70+CD38+ Patients with Chronic Lymphocytic Leukemia (CLL):
An Important Role of T-Cells in this Subgroup of CLL?**

de Beer D., Röth A., Nückel H., Sellmann L., Dührsen U., Dürig J., Baerlocher G.M. (Bern, Essen)

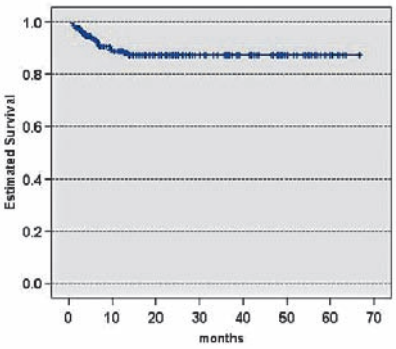
Background: Chronic lymphocytic leukemia (CLL) is not only characterized by a clonal expansion of specific B-cells, but also by an increase in non-leukemic T-cells, most likely involved in sustaining the growth of the leukemic B-cell clone. Based on ZAP-70, CD38 and the IgVH mutation status, two prognostic groups of CLL patients can be identified. Our aim was to characterize the replicative histories of the B- and T-cells in the two groups of CLL patients compared to healthy individuals.
Patients and methods: Blood samples from 73 patients with CLL (ZAP-70-CD38-: n = 29, ZAP-70+CD38+: n = 30, ZAP-70/CD38 discordant: n = 14) were analyzed. The quantity and characteristics of the lymphocyte subsets was assessed by a cell counter and by immunophenotypic analysis. The replicative histories of naive and memory T-cells as well as B-cells was determined by measurements of telomere length by automated multicolor flow-FISH.
Results: As expected the average telomere length of the clonal B-cells was short. The telomere length was, however, significantly shorter for the ZAP-70+CD38+ patient samples (2.46 ± 1.08 kb) than for the ZAP-70-CD38- patient samples (5.06 ± 1.76 kb, p <6.7 x 10-9). Interestingly, also the naive and memory T-cells from ZAP-70+CD38+ CLL patients exhibited significantly shorter average telomere lengths (mean ± std: 4.85 ± 1.58 kb; 4.39 ± 1.09 kb) than T-cells from ZAP-70-CD38- CLL patients (6.64 ± 1.72 kb, p <2.2 x 10-4 ; 6.22 ± 1.5 kb, p <7.4 x 10-6). These results are in line with the observed higher absolute T-cell numbers in the ZAP-70+CD38+ CLL patients compared to ZAP-70-CD38- CLL patients (3817 ± 3828/µl vs. 1549 ± 441/µl). When we compared the telomere length to healthy individuals (n >400, age: 0–102) practically all telomere length values of the naive and memory T-cells from the ZAP-70+CD38+ CLL patients fell below the 50th percentile, whereas the values of naive and memory T-cells from the ZAP-70-CD38- CLL patients were within the normal distribution.
Conclusions: We can confirm significantly shorter telomere length values for the B-cells of the ZAP-70+CD38+ CLL patients. In addition, we can also demonstrate significantly shorter telomeres in T-cells of ZAP-70+CD38+ CLL patients, which are below the 50th percentile compared to controls. Our observations imply an extensive expansion of the T-cell compartment in ZAP-70+CD38+ CLL patients and suggest an important role of T-cells in this subgroup of CLL patients.

S44

Outcome of chronic myeloid leukemia patients with allogeneic hematopoietic stem cell transplantation and a low risk score in the imatinib era. A report from the EBMT Chronic Leukemia Working Party and the European Leukemia Net

Heim D., Brand R., Olavarria E., Apperley J., Crawley C., Devergie A., Aljurf M., Holowiecki J., Ruutu T., Brinch L., Kolb H., de Witte T., Hehlmann R., Gratwohl A. (Basel, Leiden, London, Cambridge, Paris, Riyahd, Katowice, Helsinki, Oslo, Munich, Nijmegen, Mannheim)

Allogeneic hematopoietic stem cell transplantation (HSCT) as first line therapy for patients with chronic myeloid leukaemia (CML) has been replaced by imatinib. The role as second line therapy in patients who failed imatinib treatment is a matter of debate. Second generation Tyrosine Kinase Inhibitors (TKI) have already proven their efficacy in this setting. Early transplant related mortality of allogeneic HSCT is considered to be too high. However, no outcome data on recently transplanted CML patients has been published. In order to better counsel patients with a HLA-identical sibling confronted with this situation we performed a retrospective analysis of transplants reported to the EBMT between 2002 and 2005. We selected for patients who had a low risk score for transplant related mortality and who were transplanted from an HLA identical sibling. We analysed the outcome of those only who were transplanted in 1st chronic phase and who received best current treatment, defined as standard conditioning, no T-cell depletion and bone marrow as stem cell source. 214 patients (8% of all 2737 patients transplanted for CML in this time period) with a median follow up of 12 months (0–60 months) who fulfilled these criteria were identified. They were 46% males and 54% females with a medium age of 31 years (range 6 to 59 years). 21% (46 patients) were less than 20 years old and 20% were above the age of 40. The time interval from diagnosis to transplantation was less than 1 year in 86% of patients. About one third each had an EBMT risk score 0, 1 or 2. Data were obtained from 81 teams in 33 countries. The probability of survival at 5 years in a competing risk model was 88% (95% c.i. 83-93) with a cumulative incidence of death without relapse of 10% at 14 months and no additional death from transplant related mortality thereafter until 60 months of follow-up (Figure 1). 5-years post HSCT, 27% of patients were estimated to be alive after relapse (and hence the relapse free survival was 61%). These results show the current transplant outcome which is achievable by selecting only patients with a low risk for transplant related mortality. In this context, the data shown is valid even without information on pre- and/or posttransplant therapy. Allogeneic HSCT is a valuable option as second line therapy after imatinib failure for CML patients with a low transplantation risk.
Figure 1



S45

Impact of H-Y as a minor histocompatibility antigen in kidney transplantation

Gratwohl A., Döhler B., Stern M., Opelz G. (Basel, Heidelberg)

Background: A higher risk of graft-versus-host disease in male recipients of female grafts, an increased risk of rejection of male grafts in female recipients, and specific T-cell and antibody reactivity against H-Y encoded gene products have been documented in haematopoietic stem cell transplantation. In kidney transplantation, in contrast, the role of H-Y as a minor histocompatibility antigen has been disputed.
Patients and methods: We investigated the probability of graft survival in 202,304 recipients of a deceased donor allograft transplanted between 1985 and 2004. Using multivariate statistical methods, we compared 1- and 10-year graft survival rates of female or male donor kidneys in female or male recipients.
Results: Multivariate analysis revealed complex gender influences: female gender of donors was identified as a significant factor of graft loss (p <0.001) on both time periods. Female gender of recipients was associated with a decreased graft failure rate during the period from 2–10 years (p <0.001). Compared with all other gender combinations, male donor kidneys transplanted into female recipients was associated with a significantly increased risk of graft failure during the first year (hazard ratio HR = 1.07, 95% confidence interval CI 1.03–1.12, p = 0.002; death censored: HR = 1.10, CI 1.04–1.16, p <0.001) as well as during the years 2–10 (HR = 1.07, CI 1.02–1.11, p = 0.001; death censored: HR = 1.10, CI 1.05–1.16, p <0.001).
Conclusions: These findings provide the missing link between haematopoietic stem cell transplantation and solid organ transplantation. They are indicative of a significant HY effect in clinical kidney transplantation. They confirm the role of HY as a clinically relevant minor histocompatibility antigen in organ transplantation, solid organ and hematopoietic stem cell transplantation, in general. They provide an argument for more close cooperation between solid organ transplant physicians and hematologists as it is pllend with the Swiss Transplant Cohort Study.

S46

Severe donor events after allogeneic hematopoietic stem cell donation

Halter J., Kodera Y., Urbano Ispizua A., Greinix H.T., Schmitz N., Favre G., Baldomero H., Niederwieser D., Apperley J.F., Gratwohl A. (Basel, Nagoya, Sevilla, Wien, Hamburg, Leipzig, London, Basel for the EBMT activity survey office)

Background: The risk for donors of allogeneic hematopoietic stem cells (HSC) is generally considered negligible. Scattered reports of severe complications and a recent controversy on hematopoietic malignancies after GCSF administration for peripheral stem cell donation have challenged this opinion.
Methods: In two consecutive retrospective surveys conducted in 2003 and 2006, 338 allogeneic transplant teams from 38 European countries were asked to report their donor deaths, severe adverse events (SAE's) and hematological malignancies in a donor.
Findings: 262/338 teams (77.5%) responded to the first survey (1993–2002) and 169/262 (65%) teams to the second one (2003–2005). They performed a total of 51'024 first allogeneic hematopoietic stem cell transplantations (HSCT), 27'770 bone marrow (BM) and 23'254 peripheral blood (PB) HSCT. They observed five donor deaths, 1 after BM and 4 after PB donation (incidence 0.98 per 10'000 donations; 95% CI 0.32–2.29), 37 SAE's (7.25/10'000; 95% CI 5.11–9.99), 12 in BM (4.32/10'000; 95% CI 2.24–7.75) and 25 in PB donors (10.76/10'000; 95% CI 6.97–15.85; p <0.02). Total observation time is 300'661 person-years. 20 hematological malignancies, 8 after BM and 12 after PB donation were reported. Incidence rates for developing hematological malignancies were 0.40 per 10'000 person-years for BM and 1.20 per 10'000 person-years for PB donation. Related PB donors are about 10 years older and related and unrelated PB donors have a shorter follow up. This observed incidence corresponds to the expected incidence in an age and sex adjusted population (SEER data).
Conclusion: HSC-donation is associated with a small but definite risk for death and SAE's. Donors have to be informed even if the risks are small. Hematological malignancies do occur in BM and PB donors. There are no indications that these events exceed the risk of a normal population. The higher event rate in PB donors is likely to be explained by their higher age. These data underline the need for a continuous life long standardized donor follow up.

S47

Occurrence of autoimmune diseases before or after severe aplastic anemia diagnosis. Is there any connection?

Stalder M., Rovó A., Halter J., Heim D., Arber C., Buser A., Meyer Monard S., Rischewsky J., Stern M., Tichelli A., Gratwohl A. (Basel Stem Cell Transplant Team)

Acquired aplastic anemia (AA) is considered a T-cell mediated autoimmune disorder (AID). Its association with other AID has been described. The link between both types of AID and the impact of the AA treatment on the concomitant AID remain unclear. We conducted a retrospective single centre cohort study of 243 patients with severe AA (SAA) treated between 1974 and 2006 at the University Hospital of Basel. We looked for other AID, diagnosed before and after SAA, its prevalence and possible risk factors. Only clinical AID defined according to international diagnostic criteria were included. Patients with isolated elevation of antibody titers without further clinical signs of a disease were not included. Treatment strategy was uniform throughout the observation period. Patients below the age of 40 years (y) with a matched sibling donor (57 patients, 23%) received allogeneic hematopoietic stem cell transplantation (HSCT), all others, 186 patients (77%) were treated with antithymocyte globulin (ATG) with or without Cyclosporin A as primary therapy. Due to refractoriness or relapse, 30% needed further therapies. The median age was 22 y (2-80 y). 115 patients (47%) were female. The median follow up time was 9.4 y (0–33 y). AID was diagnosed in 24/243 patients (10%), 9 of them (37.5%) were female. Four patients had more than one AID. Autoimmune gastritis and autoimmune thyroiditis were the most frequently found AID (6 patients each). Amongst the analyzed factors for an association with AID (age at diagnosis of SAA, sex, severity of the AA, presence of HLA-DR15, type of first-line therapy, splenectomy and follow up time) only age showed a significant association. The median age was 51.5 y (9-75y) in patients with, versus 20 y (1-80y) (p = 0.00013) in patients without AID. All 13 patients with AID before SAA were treated with ATG. 2/12 showed remission of both diseases, AID and SAA; whereas in 10 patients the AID persisted. Concomitant AID did not impair outcome of SAA. After ATG therapy, an AID was diagnosed in 11 patients, with a median time to occurrence of 7 y (0.03–27.5y). Two patients developed AID after HSCT, in both the donors did not have an AID. In conclusion, simultaneous AID is seen in 10% of patients with SAA. Coincidence is unlikely to be sufficient explanation. Response to therapy in contrast, is independent and AID can persist despite full remission of SAA. This indicates that SAA and AID most likely are triggered by independent immune mechanisms.

S48

Angiogenesis and VEGF-/Receptor expression in myeloproliferative diseases: correlation with clinical parameters and JAK2-V617F mutational dtatus

Medinger M., Gratwohl A., Theocharides A., Buser A., Heim D., Skoda R., Dirnhofer S., Tichelli A., Tzankov A. (Basel)

Angiogenesis is essential for malignant tumor growth. This has been documented for solid tumors and there is emerging evidence that progression of haematological malignancies also depends on the induction of new blood vessels. The most important pro-angiogenic factor is vascular endothelial growth factor (VEGF), activating the VEGF receptor 1 (VEGFR-1) and receptor 2 (VEGFR-2). Therefore VEGF and its receptors may provide a target for therapy in hematological malignancies. In Bcr-Abl negative myeloproliferative diseases (MPD) there are only few data about the role of angiogenesis. We studied 100 patients with MPD, including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) by immunohistochemical assessment of microvessel density (MVD) and the expression of VEGF and its receptors VEGFR-1, VEGFR-2 and VEGFR-3 in bone marrow (BM) sections (table 1). The normal controls (NC) consisted of 10 BM which were free of abnormalities. MVD, as assessed by CD34 staining, was calculated as the mean number of stained vessels in 5 fields at 200 magnification. Expression of VEGF/-receptors was assessed as mean of the number of positively staining cells in 5 fields. Our study showed a significantly higher degree of angiogenesis in PMF, PV and ET compared with NC (table 1; $P < 0.001$, $P < 0.0007$ and $P < 0.001$, respectively). Angiogenesis was higher in PMF than PV and ET ($P < 0.001$ and $P < 0.001$). Increased angiogenesis correlated with higher VEGF expression compared to NC ($P < 0.009$). VEGFR-2 expression was significantly higher in MPD than in NC ($P < 0.001$) and, in particular, in PMF ($P < 0.001$) and PV ($P < 0.001$). There were no significant differences between VEGFR-1 and VEGFR-3 expression compared to NC. MVD and VEGF expression was significantly higher in JAK2-V617F mutation positive MPD [30 (12-39) vs. 22 (9-31) mean vessels per 1 mm^2 field (range); $P < 0.001$ and 49% (20–65) vs. 32% (19–42) mean %VEGF positive (+) cells (range); $P < 0.001$] than in negative MPD, but there was no difference regarding VEGF receptors expression. In conclusion, this study showed increased angiogeneis in MPD patients as expressed by increased VEGF and VEGFR-2 expression. Patients with the JAK2-V617F mutation had a higher MVD and VEGF expression than patients without the JAK2-V617F mutation. Our data support the hypothesis of an autocrine VEGF/VEGFR-2 loop in the pathogenesis of MPD. Inhibition of angiogenesis could constitute a novel strategy for the treatment of MPD.

Table 1

Table 1: Clinical characteristics, microvessel density (MVD), VEGF (vascular endothelial growth factor) and receptors expression of 100 patients with myeloproliferative diseases [(polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and normal controls (NC)].

	PMF (n=45)	PV (n=30)	ET (n=25)	NC (n=10)
Age years (range)	59 (37-68)	64 (48-70)	60 (24-72)	62 (45-68)
Sex (M/F)	25/20	18/12	10/15	5/5
MVD Mean vessels per 1 mm^2 field (range)	32 (13-79)	19 (11-59)	17.5 (7-23)	8 (1-15)
VEGF Mean %VEGF(+) cells (range)	51 % (10-75)	46% (15-70)	50% (10-75)	5% (0-9)
VEGFR-1 Mean %VEGFR-1 (+) cells (range)	22 % (5-42)	30% (7-52)	28% (6-49)	20% (2-39)
VEGFR-2 Mean %VEGFR-2 (+) cells (range)	49 % (8-69)	52% (12-79)	46% (15-63)	22% (0-9)
VEGFR-3 Mean %VEGFR-3 (+) cells (range)	20 % (3-42)	18% (0-39)	24% (10-75)	15% (0-23)

S49

Targeted disruption of GAS6-Mertk pathway leads to defects in physiological clearance of expelled nuclei from erythroblasts by bone marrow macrophages

Kadi L., Burnier L., Sugamele R., Carmeliet P., Lemke G., Earp H.S., Matsushima G.K., Schapira M., Angelillo-Scherrer A. (Lausanne, Leuven [Belgium], La Jolla CA (USA), Chapel Hill NC (USA)

Late in erythropoiesis, nuclei are expelled from erythroblasts and engulfed by macrophages in the blood island. Expelled nuclei expose phosphatidylserine (PS), which is used as an “eat me” signal for their engulfment by macrophages. PS opsonins milk-fat-globule EGF8 (MFG-E8) and GAS6 together with their respective receptors avb5 (and avb3) and Axl/Mertk/Tyro3 are involved in the phagocytosis of apoptotic cells. Because fetal liver and bone marrow macrophages do not express MFG-E8, GAS6-Mertk pathway might constitute the main pathway for the engulfment of nuclei expelled from erythroblasts. To test this hypothesis, we isolated nuclei from splenic late-stage erythroblasts and tested the capacity of bone marrow-derived macrophages (BMDM) from mice deficient in GAS6 (GAS6-/-), Axl (Axl-/-), Mertk (Mertkkd), Tyro3 (Tyro3-/-) to internalize these nuclei. Nuclei were obtained after disconnection from reticulocytes by mechanical shaking and identified by flow cytometry according to their size and their positive staining for the erythroid lineage marker Ter119 and Annexin V for PS labelling. Purity of the preparation was double-checked by morphological examination. BMDM isolated from wild-type (WT) controls and GAS6-/-, Axl-/-, Mertkkd, Tyro3-/-, Axl/Tyro3-/-, Axl-/-/Mertkkd mice were incubated with nuclear preparation, washed to remove un-engulfed nuclei, analyzed in bright field and stained with May-Grünwald-Giemsa. Phagocytosis was determined by counting the number of BMDM with ingested nuclei and the phagocytosis index revealed the number of engulfed nuclei per macrophage. We found that GAS6-/- BMDM cleared 30% less nuclei than WT BMDM ($p < 0.01$). We observe a slight decrease of internalization capacity for Axl-/- BMDM, whereas Tyro3-/- BMDM engulfed the nuclei as efficiently as WT BMDM. In contrast, Mertk deficiency nearly abolished nuclei phagocytosis ($p < 0.001$). Axl/Tyro3-/- and Axl-/-/Mertkkd BMDM were tested in comparison with WT BMDM and single knockouts, and did not show any cumulative effects when compared to single knockouts. Thus, Mertk was critical for the phagocytosis of nuclei from erythroblasts whereas the role of Axl and Tyro3 appeared to be negligible. In conclusion, GAS6 and Mertk are involved in late erythropoiesis when nuclei are expelled from the erythroblasts and engulfed by BMDM in the blood island. Indeed, GAS6 binding to nuclei exposing PS on their surface might form a bridge between PS and Mertk on BMDM, allowing their efficient clearance.

S50

The effect of DDAVP on platelet function: Enhancement of procoagulant COAT platelet formation

Conte T., Pavicic M., Barizzi G., Lämmle B., Keller P., Alberio L. (Bern)

Introduction: Desmopressin (DDAVP) is clinically efficacious in patients with disorders of the platelet function. This effect might be mediated by the release of von Willebrand factor (VWF) from endothelial cells. However, the documented efficacy of DDAVP in patients with Bernard-Soulier syndrome who lack the GPIb-IX-V complex (the platelet receptor for VWF) suggests that other mechanisms may be involved.
Methods: We investigated platelet function by flow-cytometry in 6 patients with a bleeding diathesis who received a test dose of DDAVP (0.3 mg/kg body weight). Following phenotypic and functional platelet characteristics were studied (at baseline and 2 hours after DDAVP): 1) Surface glycoprotein (GP) Ib and GPIIb-IIIa (fibrinogen receptor). 2) Content of delta-granules and their secretion upon platelet activation by thrombin (T). 3) Secretion of alpha-granules and GPIIb-IIIa activation by graded concentrations of ADP, convulxin (CVX, a specific agonist of the collagen receptor GPVI), or T. 4) Generation of procoagulant COAT platelets induced by combined activation with CVX and T (Blood 2000;95:1694).
Results: 1) Surface-expression of GPIb *increased* by 8.5% (median), GPIIb-IIIa did not change. 2) Delta-granules content *decreased* by 2.2% and their T-induced secretion *increased* by 6.3%. 3) Secretion of alpha-granules and GPIIb-IIIa activation by ADP *decreased* by 26.7% and 19.5% respectively; both end-points induced by CVX *decreased* by 29.0% and 8.3%; secretion of alpha-granules induced by T *decreased* by 13.7% and GPIIb-IIIa activation *increased* by

2.2%. 4) Percentage of generated COAT platelets *increased* by 45.2% and the intensity of negatively charged phospholipids expressed on their surface *increased* by 35.0%.
Conclusion: We show that DDAVP selectively and markedly enhances the ability to form COAT platelets. Therefore, the beneficial haemostatic effect of DDAVP is not limited to an increase in large VWF multimers; an increased platelet procoagulant activity appears to be an additional and – at least in platelet disorders – possibly more important mechanism.

S51

Dosing lepirudin in patients with heparin-induced thrombocytopenia and various degrees of renal function impairment

Tschudi M., Lämmle B., Alberio L. (Bern)

Introduction: Heparin-induced thrombocytopenia (HIT) is a severe prothrombotic complication of heparin treatment. Lepirudin is a direct thrombin inhibitor approved for its treatment. Late in 2000 we observed that patients receiving the recommended doses of lepirudin were over-anticoagulated.
Methods: Starting in 2001 we treated 51 consecutive patients diagnosed with HIT administering lepirudin without initial bolus and reducing the recommended dose by 1/3. In addition, lepirudin dose was further adjusted according to the calculated creatinine clearance (CCL). The intensity of anticoagulation was monitored with thrombin times (TT) and aPTT, its efficacy was assessed with measurements of the platelet count (PC) and D-dimers (DD).
Results: Patients with a normal renal function (CCL >60 ml/min) which had TT within the therapeutic range at first monitoring 4 hours after lepirudin start (15/29) received a median lepirudin dose of 0.087 mg/kg/h. The efficacy of this treatment was documented by a median aPTT-prolongation of 2.03 times at first control, by a PC increase from median 75 G/l at d0 to 115 G/l (d1), 137 G/l (d3), 232 G/l (d5) and by a decrease of DD from median 4599 µg/l at day 0 to 1810 µ-g/ml at follow-up. Patients with a moderately impaired renal function (CCL 30–60 ml/min) which had therapeutic TT at first monitoring (5/15) received a median lepirudin dose of 0.040 mg/kg/h. The efficacy of this treatment was documented by a median aPTT-prolongation of 2.09 times, by a PC increase from median 52 G/l (d0) to 93 G/l (d1), 164 G/l (d3), 204 G/l (d5) and by a decrease of DD from median 3634 µ-g/l to 1540 µ-g/ml. Patients with a severely impaired renal function (CCL <30 ml/min) which had therapeutic TT (6/7) received a median lepirudin dose of 0.012 mg/kg/h. The efficacy of this treatment was documented by a median aPTT-prolongation of 2.11 times, by a PC increase from median 54 G/l (d0) to 74 G/l (d3), 173 G/l (d5) and by a decrease of DD from median 2508 µ-g/l to 1568 µ-g/ml.
Conclusion: The reported data confirm that the recommended dosage schedule for lepirudin is to high. According to our experience, it is safe to avoid the initial bolus and to administer about 0.08 mg/kg/h to patients with normal renal function, about 0.04 mg/kg/h for those with moderate impairment and about 0.01 mg/kg/h for those with severe impairment of renal function.

S52

Increased variation in the autoantigen *ADAMTS13* is associated with the development of pathogenic autoantibodies in acute acquired TTP

Meyer S.C., Largiadèr C.R., Jin S., Zheng X.L., Dahinden C.A., George J.N., Lämmle B., Kremer Hovinga J.A. (Bern, Philadelphia, Oklahoma City)

Background: Acquired thrombotic thrombocytopenic purpura (TTP) is an autoimmune disorder caused by autoantibodies against ADAMTS13, the protease regulating von Willebrand factor multimeric size. The syndrome is characterized by life-threatening microvascular thrombosis. Acquired TTP represents an excellent human disease model to investigate the characteristics of a single autoantigen which contribute to the development of an autoimmune response. Therefore, we searched for particularities in the ADAMTS13 autoantigen in patients with acquired TTP.
Methods: We analyzed the *ADAMTS13* gene in 37 patients with acute TTP and acquired severe ADAMTS13 deficiency, and in 60 healthy controls. Furthermore, 15 short tandem repeats (STR) not linked to the *ADAMTS13* gene were analyzed. *ADAMTS13* haplotypes were identified based on genotypic data of 25 *ADAMTS13* polymorphisms. The inter-allelic variation was assessed by counting the heterozygous positions for 25 *ADAMTS13* polymorphisms and 15 STR loci separately. *ADAMTS13* mutations were expressed in COS-7 cells and studied for their effect on biosynthesis, secretion and proteolytic activity.
Results: 4 patients were identified as heterozygous carriers of *ADAMTS13* missense mutations P457L, found twice, R1096H and A1145T. Expression studies revealed intact secretion of mutant ADAMTS13 in comparison to wild-type protease. Activity of P457L and A1145T was reduced to 44% and 11%, respectively, but was normal for R1096H. A particular *ADAMTS13* haplotype (designated H6) was significantly more frequent in patients ($p = 0.0053$). Moreover, *ADAMTS13* inter-allelic variation was significantly higher in patients versus controls ($p = 0.012$). Primarily, non-synonymous SNPs contributed to this phenomenon ($p = 0.0014$). Increased inter-allelic variation was restricted to and specific for the *ADAMTS13* gene, as inter-allelic variation at 15 neutral STR loci was not different between patients and controls.
Conclusions: Heterozygous *ADAMTS13* mutations are prevalent in patients with acquired TTP. P457L, R1096H and A1145T either reduce baseline ADAMTS13 activity and / or may promote autoantibody formation. The *ADAMTS13* haplotype H6 and particularly the increased inter-allelic variation represent risk factors for ADAMTS13 autoimmunity and acute acquired TTP. As autoantigens in general contain higher numbers of SNPs, increased inter-allelic variation may represent an important pathophysiological feature also in other autoimmune disorders.

S53

Healthy blood donors with a positive Coombs test: Naturally occurring anti-C3 and framework-specific, anti-idiotypic antibodies together lower complement dependent phagocytosis of the senescent red cells and thereby prolong their in vivo life span

Lutz H.U., Frey B.M., Stammler P., Kradolfer M., Alaia V. (Zürich)

Coombs-positive red blood cells (RBC) from healthy blood donors carry elevated numbers of IgG molecules, as is known for many years (for a review see: Garratty. Gerontology. 1991;37:68–94). The majority of IgG molecules was associated with dense RBC from Coombs-positive healthy blood donors. These blood donors had more dense RBC than aged-matched controls and some of their RBC were even denser than the densest cells of controls. Their densest cells were in fact older than the oldest cells of controls based on the band 4.1a/b ratio. Phagocytosis of senescent RBC from these donors was 1.5 to 2 fold higher than that of senescent control cells, implying that Coombs-positive old RBC carried more opsonins. In contrast to this, their old RBC were less efficiently phagocytosed than senescent control cells in an in vitro assay in which FcR-mediated phagocytosis was suppressed by physiological concentrations of whole human IgG. The additional IgG molecules on Coombs-positive RBC from healthy blood donors comprised anti-C3 and framework-specific anti-idiotypic naturally occurring antibodies (NAbs), which were elevated in plasma of these blood donors. Hence, binding of anti-C3 together with framework-specific anti-idiotypic NAbs to senescent RBC may have suppressed their complement-dependent phagocytosis and prolonged their in vivo life span. Suppression of complement-dependent phagocytosis was achieved by binding of this pair of NAbs to senescent RBC via two possible modes: 1) by binding to senescent cell-associated anti-band 3 NAbs (Lutz, Fasler, Stammler, Bussolino, and Arese. Blood Cells 1988;14:175–195), which otherwise would have preferentially captured C3b (Lutz, Stammler, and Fasler. J. Biol.Chem. 1993;268:17418–17426), and 2) by binding to otherwise cell-associated C3 fragments.

S54

Transmigration and trapping of activated human T lymphocytes in a closed environment under mesenchymal multipotent stromal cells (MSC) are required for their inhibition in vitro

Kindler V., Granavel C., Suva D., Brouwers N., Passweg J. (Genève)

MSC are post natal stem cells that differentiate into many cell lineages and can control allogenic T lymphocyte (TL) stimulation. Such a property has been used to inhibit steroid-resistant graft versus host disease (GVHD) that may occur after allogenic hematopoietic stem cell transplantation (HSCT). Recently we showed that MSC-driven inhibition was associated, in vitro, with TL transmigration through the MSC layer (J Cell Physiol ahead pub, sept 2007). We further investigated this issue to assess whether other mechanisms were involved in TL inhibition. CFSE-labeled, highly purified TL were seeded over allogenic MSC previously plated in regular 24-well plates, or in chambers whose basement consisted in 0.2 or 3.0-micron pore-sized membranes (mm), in presence or absence of TL mitogens (PHA+IL-2, anti-CD3 and -CD28 mAb immobilized on beads). TL proliferation was assessed after 5 days by monitoring CFSE dilution. In coculture with 3-mm, TL migrated from 48 hours on through the MSC layer and the membrane. After 5 days of culture with mitogens, TL recovered in the lower chamber had significantly proliferated, and were only marginally inhibited by MSC. When 0.4-mm were used, TL did not cross the membrane and remained tightly associated with MSC, as trypsination was necessary to harvest them. Despite their localization nearby the MSC, these TL responded efficiently to mitogens, and were only marginally inhibited by MSC. By contrast duplicate cultures performed in regular hard plastic-bottomed wells showed that MSC were fully inhibitory in such a setting. These observations demonstrate that TL inhibition occurs only when transmigration targets TL under MSC bound to a waterproof surface. When TL transmigrate under MSC that adhere to a membrane allowing metabolite exchange (0.4mm), or when TL can run away from MSC after transmigration (3mm), no significant inhibition ensues. This suggests that TL have to be sequestrated for at least 48 hours in a hermetically sealed volume under MSC in order to be inhibited. This is consistent with the observation that MSC induce TL inhibition via the activation of the intracellular enzyme indoleamine 2,3 oxygenase that metabolizes L-tryptophan. Small sealed volumes under – or engulfed in – MSC certainly represent a privileged environment to induce efficient L-tryptophan depletion and LT inhibition. These data suggest that infused MSC may transiently build up a similar microenvironment to inhibit GVHD in leukemic patients.

S55

CLLU1 expression distinguishes chronic lymphocytic leukemia from other lymphoproliferative disorders

Oppliger Leibundgut E., Dissler D., de Beer D., Schuller J., Röth A., Baerlocher G.M. (Bern, Essen)

Distinction of chronic lymphocytic leukemia (CLL) from other lymphoproliferative disorders, especially from leukemic forms of mantle cell or marginal cell lymphoma, can be a challenge, and the correct diagnosis has important prognostic and therapeutic implications. Recently, the novel gene CLLU1 has been shown to be exclusively upregulated in CLL cells, and its expression has prognostic significance in CLL. We aimed to assess the specificity and sensitivity of CLLU1 expression and its utility to distinguish CLL from other B-cell lymphoproliferative disorders. CLLU1 expression was measured by quantitative RT-PCR in a total of 96 patients with lymphoproliferative disorders including CLL (n = 71), mantle cell lymphoma (n = 14), diffuse large B-cell lymphoma (n = 5), follicular lymphoma (n = 5) and marginal cell lymphoma (n = 1). Based on the CLLU1 expression of healthy controls (n = 17), a range for normal expression was defined. Overexpression of CLLU1 was observed in 60/71 cases of CLL (85%). 15% of CLL cases and 32% of lymphomas exhibited CLLU1 expression within the normal range. Interestingly, in the majority of the lymphoma patients (17/25), no CLLU1 expression was detectable. Our results demonstrate a specific expression pattern of CLLU1 in lymphoproliferative disorders: CLLU1 was high in patients with CLL (Median: 185.2, range: 0.08-18879), low in patients with non-Hodgkin lymphoma (Median: 0.0001, range: <0.0001–8.7) and intermediate in healthy controls (Median: 0.53, range: 0.02-3.2). All three groups differed significantly from each other ($p < 0.01$). CLLU1 overexpression was highly specific for CLL (specificity = 0.96, positive predictive value = 0.98), whereas absent CLLU1 expression was highly predictive for non-Hodgkin lymphoma (specificity = 1, positive predictive value = 1). Clinically, high CLLU1 expression has been shown to identify patients with an unfavorable disease. In our cohort of CLL patients, high CLLU1 was significantly associated with bad prognostic markers such as unmutated IgVH ($p < 0.01$), CD38, ZAP70, del(17p) and del(11q), confirming the prognostic value of this marker. We conclude that CLLU1 overexpression is highly specific for CLL, and lack of CLLU1 expression is significantly associated with non-Hodgkin lymphomas. Analysis of CLLU1 expression by RT-PCR is a simple novel diagnostic tool that enables distinction of CLL from other lymphoproliferative disorders, especially in cases where known diagnostic parameters fail to establish the diagnosis.

S56

Expression of cyclin A in childhood acute lymphoblastic leukemia cells reveals no evidence for a disturbed G1/S phase transition and passage through S phase

Hirt A., Schmid A.-M., Julmy F., Leibundgut K. (Bern)

Acute lymphoblastic leukemia (ALL) of childhood is characterized by a loss of cell differentiation with retained proliferative activity. The majority of ALL cells reside in the G1 phase of the cell cycle and express a hyperphosporylated form of the retinoblastoma protein (Rb). This suggested a position in late G1 phase at or beyond the restriction point resulting in a commitment to mitosis and an unresponsiveness to differentiation-inducing agents. Cells in late G1 phase should be prepared to enter S phase and, therefore, the assessment of cyclin A expression starting at the G1-S phase transition was of interest. Expression of cyclin A in ALL cells was tightly correlated with the percentage of cells in S phase as determined by bromo-deoxy-uridine (BrdU) incorporation ($r = 0.981$; $p < 0.0001$). Flow cytometric analyses of ALL cells stained with a fluorescent anti-cylin A anibody confirmed that positive cells had a higher than modal DNA content. To corroborate these findings smears were simultaneously stained for cyclin A expression and BrdU incorporation. Of all BrdU-positive S phase cells, 97.2 ± 1.4% (mean ± 1SD) were positive for cyclin A, compared with only 1.1 ± 0.5% cyclin A expressing cells in the non-S phase cell population (G0/G1 or G2). Of all cyclin A-positive cells, 10.3 ± 3.2% were not in S phase and by morphology corresponded to large blast cells, assumed to be in G2 phase. Together with the flow cytometric analyses these results confirmed that cyclin A expression in ALL cell populations was restricted to S and G2 phase cells and that there was no evidence of a disturbed expression of cyclin A in ALL cells entering and progressing through S phase. It can be concluded that the accumulation of ALL cells in G1 phase is not the result of a disturbed G1-S phase transition. Taking into consideration the changed substrate specificity of cyclin D/cdk4,6 kinase in ALL cells described earlier, hyperphoshorylation with a partial inactivation of Rb functions could occur already in mid G1 phase resulting in a loss of differentiation but not yet in a commitment to mitosis.

S57

Blocking the tumor suppressor Hypermethylated In Cancer 1 (HIC1) impairs neutrophil development and its low expression in AML is not due to hypermethylation

Jenal M., Britschgi C., Britschgi A., Torbett B.E., Tobler A., Fey M.F., Tschan M.P. (Bern, La Jolla)

A hallmark of acute myeloid leukemia (AML) is a block in differentiation caused by deregulated gene expression. *HIC1* is a transcriptional repressor, which is epigenetically silenced in solid cancers. We found HIC1 mRNA expression to be significantly low in 128 patient samples of AML and $CD34^+$ progenitor cells when compared to terminally differentiated granulocytes. Furthermore, HIC1 mRNA was induced in a patient with t(15;17)-positive acute promyelocytic leukemia (APL) receiving all-trans retinoic acid (ATRA) therapy. We therefore asked whether *HIC1* plays a role in granulocytic differentiation and whether *HIC1* loss-of-function might contribute to the differentiation block in AML. We evaluated HIC1 mRNA levels in NB4, HL-60 and U-937 cells upon ATRA-induced differentiation and in $CD34^+$ progenitor cells after G-CSF-induced differentiation. In all models of granulocytic differentiation we observed significant HIC1 induction. When HIC1 mRNA was suppressed in HL-60 cells using stably expressed short hairpin RNA targeting HIC1, granulocytic differentiation was altered as assessed by CD11b expression. Bisulphite sequencing of CpG islands in the *HIC1* promoter provided evidence that the observed suppression in HL-60 and NB4 cells is not due to promoter hypermethylation. This may shed some light on earlier, controversial reports about epigenetic silencing of *HIC1* in myeloid leukemias. Generally, our findings point to a role for the tumor suppressor gene *HIC1* in granulocytic differen-

tiation. Low expression of *HIC1* may very well contribute to pathogenic events in leukemogenesis. We are currently investigating alternative silencing mechanism of *HIC1* in AML.

S58

Green tea extract EGCG causes cell death in myeloid leukemic cells and enhances ATRA-induced differentiation through upregulation of DAPK2

Britschgi A., Fey M.F., Tobler A., Tschan M.P. (Bern)

Epigallocatechin-3-gallate (EGCG), the main polyphenolic compound present in green tea, has been reported to have chemopreventive and chemotherapeutic effects in different malignancies. EGCG inhibits cell growth and induces apoptosis in cancer cells without adversely affecting normal cells. Moreover, EGCG has recently been shown to upregulate the death-associated protein kinase 2 (DAPK2) in multiple myeloma cells. We have previously identified this pro-apoptotic kinase as an enhancing factor during granulocytic differentiation and as an important cell death mediator in epithelial cancer cells. Thus, we were wondering whether EGCG might also cause cell death via DAPK2 in myeloid leukemic blast cells. We found that EGCG treatment of myeloid leukemic blasts led to a dose-dependent increase of DAPK2 mRNA and protein. This increase was accompanied by 75% cell death as measured by XTT assay and by a 4.5-fold induction of caspase3/7 activity. Knocking down DAPK2 in NB4 and HL60 acute myeloid leukemic (AML) cell lines significantly protected the cells from EGCG-induced cell death. Since we previously observed enhanced differentiation of NB4 blasts in response to *all-trans* retinoic acid (ATRA) when DAPK2 is ectopically expressed, we were asking if EGCG treatment might support ATRA-induced differentiation by further increasing endogenous DAPK2 levels. Indeed, combination treatment of ATRA and EGCG dose-dependently enhanced neutrophil differentiation compared to ATRA-treatment alone, as assessed by CD11b, CD15, G-CSF-R and C/EBPÂ expression using FACS and quantitative RT-PCR analysis. Further, knocking down DAPK2 in these cells significantly reversed enhanced differentiation. Additionally, we found that EGCG induces cell death in ATRA-resistant NB4 and HL60 cells. In summary, we show that EGCG efficiently kills leukemic blast cells via DAPK2. Moreover, EGCG enhances ATRA-induced differentiation in AML blasts most likely by killing ATRA-resistant cell populations. Currently, we are investigating whether EGCG-induced killing of ATRA-resistant cells is dependent on expression of the “green tea receptor” 67 kD laminin receptor 1 present on these cells. We conclude that application of catechins such as EGCG, may help to optimize current chemotherapeutic treatment protocols for acute promyelocytic leukemia.

S59

Meningeoma 1 (MN1) in childhood acute myeloid leukemia

Liu T., Jankovic D., Ehret D., Baty F., Rossi V., Biondi A., Schwaller J. (Basel, Monza)

Fusion genes involving the MLL1 gene such as MLL/ENL or MLL/AF4 resulting from t(11;19) or t(4;11) are frequent genetic alterations in childhood acute leukaemia. Retroviral expression of MLL/ENL in the murine bone marrow induces an acute leukaemia phenotype that strongly mimics the human phenotype. Retroviral integration site analysis demonstrated deregulation of Meningeoma 1 (MN1) expression in a mouse with acute leukaemia induced by MLL/ENL. Expression of MN1 in murine bone marrow mediates aberrant self-renewal capacity as demonstrated by serial replating assays. Transplantation of bone marrow cells expressing MN1 induced an acute myeloid leukaemia (AML)-like disease in mice after 3 months. Co-expression of MN1 with MLL/ENL significantly reduced the latency to develop a clonal AML-like disease within 30 days demonstrating functional cooperation in leukemogenesis. In order to analyze the role of MN1 in human leukaemia we determined MN1 expression by Q-PCR in a cohort of childhood acute leukaemia. Elevated MN1 expression (>2x over normal bone marrow) was found in 6/14 cases of pediatric AML. Interestingly, 9 of 10 infant leukaemias carrying MLL-X translocations showed high levels of MN1 expression. In order to study the role of MN1 in leukaemic transformation, we have identified human cell lines carrying MLL-X fusion genes that express high levels of MN1. Knockdown of MN1 expression in RS4;11 and MOLM-13 cells (MLL-X-positive AML) by lentivirally delivered specific siRNAs (or scramble siRNAs) reduced cellular proliferation and clonal expansion. As MN1 has been previously proposed to exert its function through aberrant transcription, we are currently comparing putative downstream targets in i) murine bone marrow transiently overexpressing MN1, ii) leukemic blasts induced by MN1 and iii) leukemic blasts expressing MN1 and MLL/ENL by gene expression profiling using an Affymetrix platform. Our work so far suggests that MN1 is overexpressed in a significant fraction of childhood acute leukemia and that MN1 expression plays a role for the biology of the leukemic clone as cooperating oncogene presumably by mediating aberrant self-renewal properties through a distinct yet to be determined gene expression program.

S60

The unfolded protein response is activated in AML and induces the RNA-binding protein calreticulin

Schardt J.A., Eyholzer M., Häfliger S., Helbling D., Fey M.F., Mueller B.U., Pabst T. (Bern)

Deregulation of the myeloid key transcription factor CEBPA is a common event in AML patients. We previously reported that the RNA binding protein calreticulin efficiently blocks CEBPA translation and that calreticulin is specifically induced in core binding factor (CBF) leukemias. In addition, the chaperone calreticulin is a crucial component of the unfolded protein response (UPR). The UPR is triggered by the accumulation of unfolded or misfolded proteins within the endoplasmatic reticulum (ER) leading to ER-stress. It includes the induction of chaperon genes promoting protein folding and induction of the ER-associated degradation (ERAD) system. In vitro studies suggest that the UPR is activated in various types of cancer and thereby involved in tumor development. However, the role of the UPR during leukemogenesis has not been addressed so far. Here, we determined by RT-PCR and Western blot analysis the expression of key members of the UPR in the ER such as calreticulin, GRP78, and Gadd153, as well as the induction of the XBP1 spliced variant (XBP1s) in leukemic cells at diagnosis from 100 consecutive AML patients of all subtypes. We found that the members of the UPR were induced in 18 of 100 patients (18%). AML patients with activated UPR had lower white blood cell count (8.2 vs. 23.9 G/L), less blasts in peripheral blood (46% vs. 72%), were more frequently evolving from MDS (16.5% vs. 3.5%), and were rarely detected in monocytic (M4/5) subtypes of leukemia (5.5% vs. 30%) as compared to AML patients with uninduced UPR. Remarkably, the relapse rate at two years was significantly lower in AML patients with activated UPR (28% vs. 45%). At the molecular level, we identified two complex elements in the calreticulin promoter mediating sensitivity to ER stress. In particular, activation of both elements through the ATF6 pathway cooperating with additional partner proteins appeared to be crucial for calreticulin induction in myeloid cells. Taken together, these results provide evidence that the UPR is activated in a subset of AML patients. Induction of calreticulin as a key effector of the UPR is mediated through activation of the ATF6 pathway, thereby ultimately suppressing CEBPA translation and thus leading to a block in differentiation during leukemogenesis.

S61

A distal single nucleotide polymorphism dysregulates NF-kappaB mediated activation of the myeloid key transcription factor PU.1 in AML patients

Bonadies N., Fos J., Neururer C., Fey M.F., Pabst T., Mueller B.U. (Bern)

Timely regulation of the key transcription factor PU.1 is crucial for normal hematopoiesis. We previously showed that PU.1 expression is specifically suppressed in AML-M3 patients and restored after retinoic acid treatment. In addition, targeted disruption of an upstream regulatory element (URE) located 15 kb upstream in the PU.1 promoter was reported to decrease PU.1 expression by 80% and lead to AML in mice. Here, we screened AML patients for mutations in the entire upstream regulatory element of PU.1 by direct sequencing. We detected two polymorphisms in 4 out of 120 AML patients (3.3%) and in 1 out of 141 healthy volunteers (0.7%). Both polymorphisms were localized within 10 bp in the distal homology region of the URE. In this region we identified a NF-kappaB binding site. We found that NF-kappaB p50/p65 heterodimers and p50/p50 homodimers were indeed binding to this site, and that NF-kappaB p50/p65 activated PU.1 expression through this site in the URE. Remarkably, NF-kappaB mediated activation was abolished by the polymorphisms detected in AML patients. Furthermore, NF-kappaB synergistically activated PU.1 together with CEBPbeta whereas this synergy was lost in the presence of the polymorphisms. Finally, AML patients with the polymorphic NF-kappaB sequence showed suppressed PU.1 mRNA expression. Our results demonstrate that NF-kappaB mediated activation of PU.1 is deregulated by polymorphisms in the URE of PU.1, which are more frequent in AML patients than in healthy individuals. Moreover, our study suggests that an insertion of a single base pair in a distal element critically affects the regulation of a tumor suppressor gene and thus the development of cancer.

SGH1

Homozygous *ADAMTS13* mutations in the C-terminal protease domains severely affect protein secretion and cause congenital TTP

Meyer S.C., Jin S., Zheng X.L., Lämmle B., Kremer Hovinga J.A. (Bern, Philadelphia)

Background: Thrombotic thrombocytopenic purpura (TTP) is a devastating syndrome characterized by occlusive thrombosis in the microcirculation. Severe deficiency of ADAMTS13 proteolytic activity results in persistence of thrombogenic ultra-large von Willebrand factor multimers (ULVWF). Compound heterozygous or homozygous *ADAMTS13* gene mutations cause ADAMTS13 deficiency in congenital TTP. Homozygous mutations are of particular interest in order to elucidate the correlation of causative *ADAMTS13* genotypes and clinical disease phenotypes.
Methods: We studied 4 *ADAMTS13* missense and 1 stop mutation identified in homozygous form in patients suffering from congenital TTP. Patients homozygous for W688X, R692C or C804R became manifest with serious disease in early childhood. In presence of R1060W, milder courses with adult onset were observed. G1239V was found with childhood attacks, but led to an attenuated manifestation in adulthood. Recombinant ADAMTS13 mutants were expressed in COS-7 cells and their impact on protein biosynthesis and secretion was studied. Proteolytic activity was measured by FRETS-VWF73 assay. Intracellular localization of mutant ADAMTS13 was determined by immunofluorescent microscopy.
Results: The mutants R692C, C804R, R1060W and G1239V migrated at 190 kDa like wild-type ADAMTS13, but revealed severely reduced secretion. The mutant W688X showed a molecular weight of 97 kDa and was secreted more efficiently than wild-type protease. Immunofluorescent staining showed ADAMTS13 within endoplasmatic reticulum and Golgi apparatus, consistent with the distribution of secretory proteins. All mutants had a specific activity comparable to wild-type ADAMTS13, except for the mutant W688X, which showed a severely reduced activity.
Conclusions: Our data demonstrate that all 5 *ADAMTS13* mutations are causative for congenital ADAMTS13 deficiency. The homozygous mutations at the C-terminal ADAMTS13 primarily affect secretion of the protease. However, the truncating mutation impairs enzymatic activity. Analysis of cleavage activity towards multimeric VWF under fluid shear stress will provide deeper insight into the functional significance of the C-terminal domains of ADAMTS13 and will further elucidate the role of *ADAMTS13* genotypes for the clinical presentation of congenital TTP.

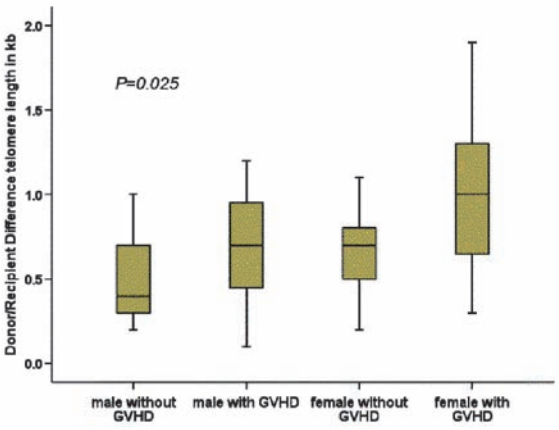
SGH2

Premature aging of hematopoietic cells in long term survivors after HSCT with chronic GVHD and a female donor

Baerlocher G.M., Rovo A., Müller A., Matthey S., Stern M., Halter J., Studt J.D., Arber C., Gratwohl A., Tichelli A. (Bern, Basel)

The establishment of donor-derived hematopoiesis in recipients of hematopoietic stem cell (HSC) transplantation (HSCT) involves extensive proliferation of HSCs and might lead to premature aging of hematopoietic cells. Telomere shortening as indicator of cell proliferation has been described after HSCT. The telomere attrition has mainly been observed during the first year after allogeneic HSCT. Thereafter, telomere length dynamics of recipients appeared not to differ from their donors. The aim of our cross-sectional study was to evaluate the telomere attrition in leukocyte subsets of very long term survivors (LTS) after HSCT in relation to donor/recipient age, sex, cell counts in peripheral blood, number of transplanted nucleated cells (NTNC), and occurrence of acute and chronic graft versus host disease (GVHD). Automated multicolor flow-FISH was used to measure the telomere length in subsets of leukocytes of 44 LTS and their HLA-identical sibling donors. At HSCT the median age of donors and recipients was 25.8 (2-46) and 26.8 years (5-50). The median follow-up after HSCT was 17.5 years (11-26). Four patients received HSCT for aplastic anemia, 40 for hematological malignancies. All patients received bone marrow as source of HSC and TBI was part of the conditioning in 39 (89%). Acute GVHD was observed in 31 (70%), and chronic GVHD in 22 (50%) patients. The telomere length (mean std) was significantly shorter in recipients as compared to their donors ($p < 0.01$) for granulocytes (6.50.9 vs 7.10.9), T-cells (5.71.2 vs 6.61.2), B-cells (7.11.1 vs 7.81.1) and NK/NKT-cells (4.81.0 vs 5.61.3). The mean telomere length of all subsets of cells was significantly shorter for males compared to females even though this difference was small. Age, sex of recipient, NTNC, and acute GVHD had no impact on telomere attrition. In all cell types we found a significant telomere shortening in recipients transplanted with a female donor ($p < 0.04$) and in those with chronic GVHD ($p < 0.04$). The telomere length difference between donor/recipient was most pronounced for recipients with the combination of a female donor and chronic GVHD (Figure 1) and is more than twice compared to those with a male donor without chronic GVHD. The more pronounced telomere attrition with a female donor and chronic GVHD corresponds to approximately 30-60 years of cell aging and raises the question of cellular immuno-senescence and its consequences in LTS of HSCT.

Figure 1



P1

An anthropological study on diabetes and vulnerable populations

Spahr N., Rossi I., Ruiz J., Bodenmann P. (Lausanne)

Background: To address the issue of a chronic condition like diabetes, it could be interesting to integrate a complementary approach between social and medical sciences. Taking into account the different social situations of patients, the two main objectives were first to study patient's perceptions around diabetes and the impact of their illness on their daily life; and secondly to compare specialists and general practitioner's perceptions and their difficulties around diabetes management with these diverse populations.
Methods: This study was an interdisciplinary qualitative research including 3 weeks of direct observation of the medical consultations, 10 individual face-to-face interviews and 4 focus groups with patients (5 migrants and 4 natives) and therapists (8 specialists and 8 physicians) of CHUV and PMU to collect information for the thematic analysis.
Results: Comparing native and migrant populations, we observed that the initial step of diagnosis has a considerable impact on patient's long term adhesion to the medical treatment. Diabetes management is related with lifestyle modifications, migration process and previous experiences, which have a significant influence on patient's compliance. For physicians, serious modifications implied by diabetes present some major difficulties and have an impact in the complexity of therapeutic management of this chronic illness: it is in particular hard to manage enough time to investigate their patient's perceptions respecting at the same time guidelines or still to evolve as guides promoting Diabetes-Self-Management. Compared to natives, migrants used strangely enough more medical references than emotional perceptions to explain their illness. Considering all these different priorities, relationships between patients and medical staff could be improved.
Discussion: The migration process and the socio-cultural diversity have an impact on the patient's perception and the management of diabetes. In their medical practice, general practitioners have a more global view to manage their patients but use less the networks of collaborators than specialists. To improve diabetes management and prevention, our study suggests to develop a systemic approach to support a better negotiation between the health professionals and the patient's environment and also to encourage the therapeutic education and transcultural competences training on medical education programs.

P2

Effet du diabète et d'une consultation spécialisée en Diabétologie sur le management du diabète dans un service de Médecine Interne

Garcia E., Nguyen S., Comte-Perret S., Gaillard R.C, Waeber G., Ruiz J. (Lausanne)

Introduction: Les patients diabétiques sont des sujets à risque de complications lors d'une hospitalisation. De nombreuses études montrent que l'hyperglycémie en soi est associée à une morbi-mortalité plus élevée et que son contrôle permet de réduire la mortalité, la durée de séjour (DS) et les coûts. Le but de l'étude est d'évaluer l'impact du diabète sur la DS et la morbi-mortalité ainsi que l'effet d'une consultation spécialisée en diabétologie (CS) sur ces paramètres.
Méthodes: Il s'agit d'une étude d'observation rétrospective portant sur 800 patients consécutifs admis directement dans le Service de MI, entre janvier et septembre 2005. Les paramètres suivants ont été évalués: motifs d'admission, DS, traitements médicaux, contrôles glycémiques, jour de la CS et morbi-mortalité. Nous avons différencié les diabétiques connus (DMC) et les diabétiques non diagnostiqués (DMND), mais répondant aux critères de l'OMS, sur la base d'une glycémie ≥11,1 mmol/l pendant le séjour.
Résultats: L'âge médian du collectif est de 74 ans (59–83), 51% sont des hommes, décès 10%. Les diagnostics principaux sont: affections respiratoires (21%), insuffisance cardiaque (12%), affections oncologiques (11%), infections (10%). La DS médiane est de 12 jours (8–17). Le groupe DMC représente le 21% des patients (n = 168), le groupe DMND 4,5% (n = 36), soit 18% de tous les diabétiques. Le taux de mortalité est de 9% dans le groupe non diabétique, 11% chez les DMC, 16% chez les DMND (p = 0,11). Dans le groupe des DMC ayant eu une CS, le taux de mortalité est de 0% vs 15% sans CS (p = 0,015). Le groupe DMC ayant eu une CS reste 4,5 jours de plus que celui sans CS (15,5 j vs 11 j, p = 0,0017). Parmi les patients ayant bénéficié d'une CS dans les 3 premiers jours, on observe que 75% d'entre eux voient leur séjour significativement diminué (p = 0,0007). Parmi les DMC, 20% n'ont pas reçu de traitement hypoglycémiant pendant le séjour, malgré un contrôle métabolique altéré.
Conclusions: Cette étude relève une DS plus longue chez les diabétiques. Parmi ces patients, 18% ont été diagnostiqués rétrospectivement. L'absence de CS n'était pas toujours justifiée par une affection terminale. La mise en place d'un programme structuré de prise en charge précoce des patients diabétiques en milieu hospitalier pourrait permettre de réduire la morbi-mortalité, la DS et par conséquent les coûts liés au diabète.

P3

L'adhérence thérapeutique: première cause de décompensations diabétiques aiguës

Nguyen S., Waeber G., Schaller M-D., Trueb L., Gaillard R.C., Ruiz J. (Lausanne)

Introduction: Les décompensations acido-cétosiques (ACD) et hyperosmolaires (EHH) sont les complications aiguës parmi les plus graves du diabète. Ces complications restent associées à des taux de mortalité élevés (ACD <5%, EHH = 15%). Le but de cette étude est d'analyser les facteurs déclenchants, les complications intra-hospitalières, le traitement, la durée de séjour (DS), la mortalité et l'impact d'une consultation spécialisée de diabétologie dans le CHUV.
Patients et méthodes: Il s'agit d'une étude rétrospective de 152 patients admis pour ACD, EHH ou décompensation acido-cétosique et hyperosmolaire (ACD-EHH) dans le service de Médecine Interne du CHUV entre 1995 et 2006. Les décompensations ont été définies selon les critères 2004 de l'ADA, i.e. ACD = glycémie plasmatique ≥14 mmol/L, pH artériel ≤7,30 et présence de corps cétoniques sanguins ou urinaires; EHH = glycémie plasmatique ≥33,3 mmol/L et osmolalité sérique ≥320 mOsm/kg, ACD-EHH = combinaison des deux.
Résultats: Age médian (p 25–75): 54 ans (37,5–76,5), sexe masculin: 53%; ACD: 62%, EHH: 22%, ACD-EHH: 16%. Principaux facteurs déclenchants: non adhérence (42%), infections (26%), diabète inaugural (18%), indéterminé (9%), cardiovasculaire (7%). Les patients non adhérents avaient plus d'ACD que d'EHH ou ACD-EHH (29,7% vs. 11,9%, OR = 1,71, p = 0,038), tout comme les diabétiques de type 1 (38,1% vs. 6%, OR = 4,49, p = 0,001). DS médiane: 9 jours (6–14), les diabétiques de type 2 étant hospitalisés plus longtemps que les types 1 (12 vs.7 j, p <0,0001). Les patients avec une ACD avaient une DS médiane plus courte que les autres (7 vs. 10 j, p = 0,037). Mortalité intra-hospitalière: ACD-EHH = 12,5%, ACD = 8,1%, EHH = 4,6%. Une consultation de diabétologie était associée à une réduction significative de la mortalité aussi bien en analyse univariée (4,5% vs. 66,7%, OR = 0,09, p <0,0001), que multivariée (p <0,0001).
Conclusion: Nous mettons en évidence pour la première fois que l'adhérence thérapeutique est la cause principale d'ACD, EHH et ACD-EHH, contrairement à la littérature où prédominaient les infections. L'ACD-EHH avait la mortalité la plus élevée, ce que nous expliquons par le plus grand déséquilibre métabolique existant dans ce groupe. Une consultation de diabétologie est associée à une diminution importante de la mortalité. Nous recommandons une évaluation éducative des patients diabétiques, ainsi qu'une consultation de diabétologie dès leur admission afin de réduire le risque de récidive.

P4

Effects of the adrenal function on endothelial integrity and on the hemostasis system in the perioperative setting

Henzen C., Studer F., Schüpfer G., Bründler J., Briner V., Brander L. (Luzern, Bern)

Background: The adequate response of the cortisol axis to stress, i.e. the rapid increase of the adrenal cortisol secretion, is essential to maintain vascular tone and endothelial function. Furthermore, the perioperative regulation of the volume balance and the amount of blood loss correlate with the adequacy of the adrenal function. In the present study we evaluated the association of the adrenal response to ACTH and markers of endothelial and hemostatic function in patients undergoing elective abdominal surgery.
Methods: A low-dose (1 mcg) ACTH test was performed on the day before surgery, during surgery (30 min after the initiation), on the day after surgery and before discharge. Patients with a history of glucocorticoid treatment or induction of anesthesia with etomidate, endocrine diseases and acute illness were excluded. Soluble vascular cell adhesion molecule-1 (sVCAM-1) and thrombomodulin were measured as markers of endothelial function. Fibrinogen, von Willebrand factor (vWF), factor VIII and thrombocytes were measured to evaluate hemostasis. Data are mean (+ SD) and median [interquartile range] resp., and differences were tested by Student's t-test and Mann-Whitney test, resp.
Results: A total of 82 patients (50 M/32 F) were included in the study. The mean age was 63,8 (15) years, the median length of the operation and of the intubation were 144 [80–165] mins and 223 [150–290] mins, resp. The median decrease of the hemoglobin was 24,8 [16,1] g/l. A deficient adrenal response to ACTH was diagnosed in 24 patients (29%). These patients had increased postoperative levels of sVCAM-1 ($p = 0,033$). However, there were no significant differences in the concentrations of thrombomodulin ($p = 0,056$), fibrinogen ($p = 0,11$), factor VIII ($p = 0,6$), vWF antigen ($p = 0,59$), and thrombocytes ($p = 0,79$) in patients with normal and deficient adrenal function. The amount of blood loss, infusions of packed red cells and fresh frozen plasma, and the hemoglobin concentrations before and after surgery were similar in patients with normal and deficient adrenal function.
Conclusion: An insufficient rise of plasma cortisol to ACTH is common in patients undergoing elective abdominal surgery. Although there may be subtle changes in the endothelial function, there were no effects on the hemostatic system and the clinical outcome in this defined stress situation.

P5

Treatment with cinacalcet in patients with surgically not resectable primary hyperparathyroidism

Widmer I., Neidert S., Simon-Vermot I., Henzen C. (Luzern)

Background: Primary hyperparathyroidism (pHPT) leading to hypercalcaemia results from excessive secretion of parathyroid hormone (PTH), in about 80% of the cases by a single parathyroid adenoma. However, in some patients pHPT persists after surgery when the parathyroid adenoma can not be localised or parathyroid hyperplasia occurs as part of familial endocrinopathies. The calcimimetic agent cincalcet reduces hypercalcaemia in patients with inoperable parathyroid carcinoma.
Methods: Our study describes the effect of the treatment with cinacalcet in patients in whom surgery of pHPT was not successful. In patients with persistent postoperative hypercalcaemia the following clinical and laboratory variables were assessed before and under treatment with cinacalcet: quality of life, psychiatric and musculosceletal symptoms; serum calcium, phosphorus and PTH levels, and calciuria. Treatment with cinacalcet aimed to lower the serum calcium concentration into the normal range. The study was approved by the local institutional ethics committee.
Results: Our cohort study comprised 5 patients (4 males). The mean age was 53.8 [30 to 65] years. The mean serum concentration of calcium before treatment was 3.1 [2.88 to 3.67] mmol/l (normal range 2.1 to 2.7), of posphorus 0.83 [0.69 to 0.98] mmol/l (normal 0.9 to 1.5), of intact PTH 480.1 [53 to 2019] pg/ml (normal 15 to 65), and the mean urinary calcium excretion was 8.9 mmol/d. Depression was diagnosed in 3/5 patients, sleeping disturbances in 2/5, muscle weakness or myalgias in 4/5, arthralgias in 4/5; osteoporosis/osteopenia in 3/5, pancreatitis in 1/5, and kidney stones in 1/5. The mean dose of cinacalcet was 144 [60 to 360] mg. The mean serum calcium concentration under treatment with cinacalcet was 2.73 [2.41 to 2.94] mmol/l, the mean PTH 465.5 [48 to 1627] pg/ml. Psychiatric and musculoskeletal symptoms disappeared apart from sleeping disturbances in 2/5 and arthralgias in 2/5. Apart from nausea (1/5) no side effects were recorded.
Conclusion: Treatment with cinacalcet is effective in reducing hypercalcaemia in patients with persistently elevated PTH secretion after surgery. Furthermore, clinical signs and symptoms of pHPT are significantly reduced.

P6

The epidemiology of pituitary adenoma: a study in an urban agglomeration of the west of Switzerland

Fontana E., Gaillard R.C. (Fribourg, Lausanne)

Enzo Fontana M.D.°*; R.C.Gaillard M.D.* °*Diabetic and Metabolic unit of the Medical Clinic, Fribourg Hospital, and *Endocrine, Diabetic and Metabolic Service; University hospital (CHUV), Lausanne, Switzerland

Introduction: Epidemiological data concerning pituitary adenomas are very scarce and in some cases reports are even conflicting. Previous papers focusing on this rare condition described a prevalence of 1 case in every 4,000–6,000 people. This opinion is at present disputed as there is some evidence of a greater prevalence than formerly believed. The aim of this study was to evaluate, in an urban area of Switzerland, the prevalence of relevant clinical pituitary adenoma in patients followed by their own doctor (GP, endocrinologist or gynaecologist).
Methods: This analysis was made on May 31st 2007 after a collection period between April 1st 2006 and May 31st 2007 in the agglomeration of Fribourg (the city of Fribourg as well as the surrounding urban districts of Givisiez, Marly and Villars-sur-Glâne, Switzerland). This agglomeration has a resident population of approximately 54607. General practitioners, endocrinologists and gynaecologists were questioned concerning any patient within this agglomeration presenting with a pituitary micro- or macro- adenoma. Others points determined were: age, sex of each patient and the existence of a neurosurgical procedure or medical treatment for this condition. 75 doctors in this area were consulted by questionnaire out of which 63 replied. 22 different doctors followed the 45 patients detected.
Results: 45 patients were reported. Of these, 44 presented a clinically significant pituitary adenoma and 1 patient had a Rathke cyst, which was excluded from the analysis. In the studied area we found a prevalence of 80.5 pituitary adenomas per 100,000. 73% of the adenomas were reported in women. Among the 44 adenomas, we observed 13 non secreting macro-adenomas, 25 prolactinomas (9 macros and 16 micros), 4 cases of acromegaly and 2 of ACTH-dependant Cushing disease.
Conclusion: Our study concords with a recent finding demonstrating a greater prevalence of pituitary adenomas than previously believed. The prevalence of this condition, in an urban area of the west of Switzerland, is 1 case per 1241 which is about a 4 fold increase compared to the prevalence given in textbooks.

P7

A reduced bmi cut-off for estimating obesity prevalence based on self-reported height and weight: a validation study

Kossovsky M., Dauphinot V., Naudin F., Wolff H., Gaspoz J.M. (Genève, Saint Etienne)

Background: The estimation of obesity prevalence and its temporal trend in the population is important when assessing public health and economic burden. It has already been demonstrated that self-reported heights and weights do not allow a correct estimation of the true prevalence of obesity.
Methods: A cross sectional study conducted in France in 2002–03 comparing self-reported with measured data showed that obesity prevalence determined by body mass index (BMI) calculated from self-reported weight and height was underestimated: 30.1% of men and 34.3% of women not considered obese according to their self-reports were classified as such by measurements. We proposed to lower the self-reported BMI threshold defining obesity to 29.0 kg/m^2 for men and 28.4 kg/m^2 for women. This yielded to an estimation of obesity prevalence similar to the one obtained using measurements (15.1% vs. 14.4%, p = 0.21) and was the best compromise between sensitivity (83.5%) and specificity (96.4%).
Results: A validation procedure was performed on a different population. From 1993 to 2004, a sample of 13,266 men and women (500 each per year) was recruited in Geneva, Switzerland. Self-reported and measured BMI were routinely collected. As already observed, almost one third (33.6% among men and 27.5% among women) of the subjects not considered obese according to their self-reports were classified as such by measurements. The reduced threshold for obesity based on self-reported data was applied and its performance compared to measured data. The reduced obesity threshold could correctly classify subjects in 95.5% of cases, with a sensitivity of 88.9% and specificity of 96.5% (Figure). Positive and negative predictive values were respectively 78.6% and 98.4%.
Conclusions: Subjects in population studies tend to underestimate their weight and to overestimate their height. This yields to erroneous obesity prevalence in populations where this estimation is based on self-reports only. Contrasting with corrective equations, this readily applicable reduced threshold does not require collection of additional data. Its applicability to other European or American countries requires further validation.

P8

MedGem – ein einfaches Gerät zur Bestimmung des Ruheenergieumsatzes

Rüfenacht U., Rühlin M., Imoberdorf R., Ballmer P.E. (Winterthur)

Einleitung: Um bei schwer Kranken eine bedarfsgerechte Ernährung zu gewährleisten ist es unerlässlich den Energiebedarf ermitteln zu können. Als Goldstandard zur Messung des Energieumsatzes gilt die klassische indirekte Kalorimetrie, deren Durchführung im Spitalalltag sehr aufwendig ist. Seit einigen Jahren ist ein handliches, indirektes Kalorimeter auf dem Markt, welches den Ruheenergiebedarf allein durch Messung des Sauerstoffverbrauchs in kurzer Zeit und unter einfacher Handhabung ermittelt. In der vorliegenden Pilotstudie haben wir die Messwerte dieser zwei Techniken verglichen.
Methoden: Es wurden gesunde Personen sowie Patienten mit verschiedenen Krankheitsbildern eingeschlossen. Zunächst wurde die Messung mit dem indirekten Kalorimeter Vmax 29n (Sensor Medics, Yorba Linda, CA, USA) vorgenommen und danach mit dem MedGem (MedGem, Healthetech, Golden, CO, USA). Beide Messungen fanden am ruhig liegenden Patienten unter gleichen und für die indirekte Kalorimetrie vorausgesetzten Bedingungen statt. Zudem wurden die klassischen Formeln von Harris-Benedict und Ireton-Jones mit den Messwerten des Vmax verglichen.
Resultate: Der Ruheenergieumsatz betrug mit Vmax bei den Gesunden (n = 11) 1531 ± 247 kcal, bei den Patienten (n = 22) 1428 ± 384 kcal, mit MedGem 1558 ± 324 kcal (p = 0,896 gegenüber Werten mit Vmax), bzw. 1482 ± 390 kcal (p = 0,481). Zwischen Vmax und MedGem bestand eine hochsignifikante positive, lineare Korrelation, sowohl bei den Gesunden (r = 0,85, p <0,001) als auch den Patienten (r = 0,88, p <0,001). Beim Vergleich mit den Formeln ergab sich ebenfalls eine signifikante Korrelation, allerdings mit tieferen Korrelationskoeffizienten.
Diskussion: Die Messungen mit MedGem korrelieren sehr gut mit denjenigen der Messung mittels klassischer indirekter Kalorimetrie. Die individuellen Werte müssen jedoch mit Vorsicht interpretiert werden, da sie deutlich voneinander abweichen können. Die Resultate sollen immer unter Einbezug der klinischen Verlaufsbeurteilung genutzt werden. Der gezielte Einsatz von MedGem beim schwer Kranken ermöglicht eine einfache und schnelle Ermittlung des Energieumsatzes im Spitalalltag.

P9

Ernährungsmanagement-Studie: Vorläufige Screening-Datenanalyse

Iff S., Leuenberger M., Gutzwiller JP., Mühlebach S., Perrig M., Stanga Z. (Bern)

Hintergrund: Mangelernährung (ME) wird bisher in den Spitälern ungenügend wahrgenommen, Risikopatienten werden nicht früh genug erfasst und werden folglich zu spät adäquat behandelt. Es fehlen fundierte Studien, welche die Wirksamkeit der Ernährungstherapie belegen.
Methode: Klinische, prospektive, randomisierte Interventionsstudie mit den Hauptendpunkten Aufenthaltsdauer und Lebensqualität. Die Studie findet auf den Abteilungen der Klinik für Allgemeine Innere Medizin des Universitätsspital Bern statt. Studiendauer: 02/07 bis 03/08. Bei Spitaleintritt wurde jeder Patient mittels Nutrition Risk Score (NRS) 2002 nach Kondrup erfasst. Die maximale Punktezahl dieser Screening-Methode beträgt 7. Eine Punktzahl ≥3 weist auf eine schwere Mangelernährung oder ein hohes Risiko für Mangelernährung hin und darauf, dass der Patient von einer Ernährungstherapie profitiert.
Bisherige Resultate: Vom 02/07 bis 01/08 wurden 1671 neueintretende Patienten (n = 100%) mittels NRS auf ME gescreent. Die Prävalenz der Patienten mit einem NRS-Gesamtscore von ≥3 betrug 51% (n = 860). Demographische Daten der Patienten (MW ± s): Alter 63,1 ± 17,9 J, Grösse 1,69 ± 0,1 m, Gewicht 73,2 ± 17,2 kg, BMI 25,4 ± 5,9 kg/m^2, NRS-Gesamtscore 2,9 ± 1,4 Punkte, Energiebedarf (Grundumsatz + 20% Aktivität) 1752 ± 336 kcal. Die Risikogruppe war signifikant älter (64,2 ± 17,7 vs. 61,9 ± 18 J, p = 0,01), hatte einen signifikant tieferen BMI (24 ± 5,7 vs. 27 ± 5,7 kg/m^2, p <0,001) und einen tieferen Energiebedarf (1679 ± 312 vs. 1835 ± 343 kcal, p <0,001). Das hohe Risiko für ME war gleich in jeder Altersgruppe. Altersmässig waren 40,5% (n = 665) der Patienten ≥70 J. Der Appetitverlust in den letzten 7 Tagen sowie der Gewichtsverlust in den letzten 3 Monaten waren die häufigsten Gründe für mehr Punkte im NRS. Nur 8% (n = 122) hatten einen hohen NRS wegen isoliert tiefem BMI (<18,5 kg/m^2). Ein leichter metabolischer Stress, bedingt durch die Grundkrankheit, wurde bei 84,9% (n = 1416) der Patienten beobachtet; 14.4% (n = 240) der Patienten hatten einen erhöhten Stressfaktor.
Schlussfolgerung: Die hohe Prävalenz der schweren ME oder des hohen Risikos für ME auf den universitären internistischen Abteilungen weist eindrücklich auf den dringenden Handlungsbedarf im Kampf gegen die ME hin. Die Frage nach Gewicht- und Appetitverlust identifiziert den grössten Teil der mangelernährten Patienten. Wie hoch der klinische Benefit der Ernährungstherapie (Outcome) sein wird, kann erst nach der Entblindung der Studie evaluiert werden.

P10

Selective Effects of High Fat Diet on Vascular Reactivity Modulates to Endothelin: Involvement of NADPH-Oxidase subunit Nox2

Damjanovic M., Rasi J., Bhattacharya I., Haas E., Barton M. (Zürich)

High dietary fat intake is associated with structural and functional alterations in the kidney, promoting development of renal diseases. The renal artery, which is central in renal perfusion, is highly sensitive to vasoactive factors. Renal endothelin-1 (ET-1) has been shown to be associated with activation of renin-angiotensin system (RAS) in the kidney in obesity. However, the role of NADPH oxidase Nox2 (gp91^{phox}) in ET-1-mediated contraction in the renal artery is not known. Therefore, the aim of this study was to find out whether Nox2 is involved in modulation of ET-1-mediated contraction in the renal and femoral artery, and whether this is affected by high-fat diet. Experiments were performed with male C57BL/6J (wild-type control and Nox 2$^{-/-}$) mice, which were fed with either standard chow or high-

fat diet (41% kcal from fat) for 15 weeks, starting at 4 weeks of age. Rings from renal artery and femoral artery were pre-incubated with nitric oxide (NO) synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME; $3x10^{-4}$ M) for 30 min, followed by treatment with ET-1 in a concentration-dependent manner (10^{-11} – 10^{-7} M). In wild-type mice on a control diet, the maximum contraction to ET-1 was similar between renal and femoral artery. Interestingly, high-fat diet reduced ET-1-mediated contractions in the renal artery ($p < 0.05$ vs. control diet) but not in the femoral artery. In Nox2-deficient animals ($Nox2^{-/-}$) on a control diet, the contraction mediated by ET-1 was reduced in the renal artery ($p < 0.05$ vs. wild-type), an effect unaffected by high-fat diet (ns). Contractions to ET-1 in the femoral artery were affected neither by high-fat diet nor by Nox2-deficiency. In conclusion, the data presented here suggests that the renal artery but not the femoral artery is highly susceptible to the changes mediated by high-fat diet and that Nox2 modulates ET-1-dependent vascular contractility only in the renal artery. This study further suggests that during the early stages of obesity the renal artery is highly sensitive and susceptible to changes, which may propagate renal dysfunction and diseases associated with it.

P11

High-fat diet increases mouse BMI and endothelial prostanoid contractions but does not impair nitric oxide bioactivity

Bhattacharya I., Damjanovic M., Perez-Dominguez A., Gut A., Hager S., Haas E., Barton M. (Zürich)

Intake of diets rich in fat is a major cause of obesity, which accelerates the development of cardiovascular diseases. The aim of this study was to establish a method to quantify mouse obesity and to investigate the effect of high-fat diet on basal nitric oxide bioactivity and on prostanoid contractility in the mouse carotid artery. Male C57BL/6J mice received either control diet (standard chow; 12.5 kcal from fat) or high-fat diet (58% kcal from fat) for 30 weeks, starting at 4 weeks of age. Analogous to human BMI (kg/(weight in m^2), mouse BMI was defined by mouse weight (g)/height $(mm)^2$. Relative insulin resistance was measured using glucose tolerance test. Vascular functional experiments were performed in carotid arterial rings treated either with or without NG-nitro-L-arginine methyl ester (L-NAME; $3x10^{-4}$ M) for 30 min followed by treatment with phenylephrine (PE; $3x10^{-8}$ M) and acetylcholine (ACh; 10^{-10}-10^{-5} M). Contractile response to PE was normalized to KCl (100 mM) and endothelium-dependent contraction was normalized to maximal PE contraction. After high-fat diet BMI increased from 30 ± 0.4 to 34 ± 0.6 ($P < 0.05$ vs. control), indicating obesity. Obese animals showed glucose intolerance ($P < 0.05$ vs. control). High dietary fat intake increased the contraction to PE ($3 x10^{-8}$ M, $P < 0.05$ vs. control) and to prostanoid-mediated endothelium-derived contracting factors, (ACh-10^{-7} M, $P < 0.05$ vs. control). In contrast, ACh-mediated endothelium-dependent relaxation was similar in control and obese animals. Treatment with L-NAME caused a 2-fold increase in PE-mediated contraction in both control and obese animals. In conclusion, we present a novel method for measuring mouse BMI. High dietary fat intake increases mouse BMI and prostanoid-mediated vascular contractility without affecting basal NO bioactivity.

P12

Low density lipoprotein-mediated vascular smooth muscle cell growth is potentiated by insulin: role of protein kinase B

Haas E., Minotti R., Raselli C., Hoehn A., Hranac M., Barton M. (Zürich)

Metabolic diseases, including diabetes and obesity, are associated with hyperinsulinemia and insulin resistance. These pathophysiologic conditions accelerate atherosclerosis development, which is associated with proliferation of vascular smooth muscle cells. This study investigated the effects of physiological levels of insulin and low density lipoprotein (LDL) on the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, protein kinase B (PKB), and insulin receptor substrate -1 (IRS-1), and on the proliferation of VSMC. Phosphorylation of signaling molecules was measured by Western blot analysis using phospho-specific antibodies, and cell proliferation was quantified by [^{3}H]-thymidine incorporation assay. Vascular smooth muscle cell proliferation was strongly enhanced by LDL (up to 5-fold, $P < 0.001$ versus control), whereas cells stimulated with insulin showed only small changes (less than 1.5-fold). In cells exposed to submaximal concentrations of LDL, the proliferative response was potentiated in the presence of insulin (approximately 3-fold, $P < 0.0001$ for LDL and insulin versus LDL alone). Insulin caused PKB phosphorylation, whereas LDL had no effect. LDL concentration-dependently inhibited insulin-induced PKB and IRS-1 tyrosine phosphorylation ($P < 0.05$ for insulin plus LDL versus insulin alone). In contrast, both insulin and LDL induced phosphorylation of ERK1/2. Interestingly, inhibition of the PKB signaling pathway in insulin-stimulated cells with the phosphatidylinositol-3-kinase inhibitor LY294002, similar to LDL inhibited PKB phosphorylation, increased insulin-mediated cell proliferation. These data indicate that physiological levels of LDL found in human plasma suppress insulin-mediated PKB activation without affecting the mitogenic ERK1/2 pathway. Since PKB signaling is required to maintain vascular smooth muscle cells in a quiescent, differentiated state, inhibiton of the metabolic insulin signaling pathway by LDL may become important in insulin resistant individuals and diabetics with concommitant hypercholesterolemia accelerating atherosclerosis development in these patients.

P13

Opposing effects of diets rich in plant or animal fat on renal regulation of genes implicated in cellular redox balance

Haas E., Winklehner A., Bhattacharya I., Minotti R., Damjanovic M., Barton M. (Zürich)

Glomerular damage is enhanced by obesity, which is associated with low-grade inflammation and increased production of reactive oxygen species (ROS). In obesity-associated renal injury the effect of plant-fat or animal-fat on expression of genes involved in redox regulation is not known. The aim of the study was to quantify and compare renal cortex gene expression of pro- and antioxidant enzymes and the inflammation-associated adhesion molecule ICAM-1 in C57BL/6J mice fed with standard diet (SD), or diets rich in animal-fat (AFD; milk fat) or plant-fat (PFD; coconut oil) for 15 weeks. Body weight was monitored and glucose tolerance (ip GGT) was determined. Feeding of both high-fat diets resulted in a comparable weight gain and glucose intolerance (n.s., AFD vs. PFD). In the renal cortex, the expression levels of the pro-inflammatory genes (NO synthase 2, NOS2; catalytic subunit of the phagocytic NADPH oxidase, Nox2; intracellular adhesion molecule-1, ICAM-1) were more than 30-fold lower compared to anti-oxidant genes (gluthatione peroxidase, GPX and Cu/Zn superoxide dismutase, SOD1) and the regulatory subunit of the NADPH oxidase complex p22*phox*. Treatment with AFD but not with PFD increased mRNA expression of NOS2, Nox2, and ICAM-1. Interestingly, PFD but not AFD treatment was associated with upregulation of the antioxidant genes SOD1 and GPX and reduction of p22*phox*. In conclusion, these data suggest that plant-fat diet, in contrast to animal-fat diet, may contribute to an anti-oxidative/inflammatory state in the renal cortex despite development of obesity.

P14

Relationship between cigarette smoking and abdominal obesity

Willi C., Chiolero A., Faeh D., Cornuz J., Marques-Vidal P., Paccaud F., Waeber G., Vollenweider P. (Lausanne)*

Background: Although smokers tend to have a lower body-mass index (BMI) than non-smokers, smoking may affect body fat (BF) distribution. Some studies have assessed the association between smoking, BMI and waist circumference (WC), but, to our knowledge, no population-based studies assessed the relation between smoking and BF composition. We assessed the association between amount of cigarette smoking, BMI, WC and BF composition.
Method: Data was analysed from a cross-sectional population-based study including 6'187 Caucasians aged 32–76 and living in Switzerland. Height, weight and WC were measured. BF, expressed in percent of total body weight, was measured by electrical bioimpedance.

Abdominal obesity was defined as a WC ≥102 cm for men and ≥88 cm for women and normal WC as <94 cm for men and <80 cm for women. In men, excess BF was defined as %BF ≥28.1, 28.7, 30.6 and 32.6 for age groups 32–44, 45–54, 55–64 and 65–76, respectively; the corresponding values for women were 35.9, 36.5, 40.5 and 44.4. Cigarette smoking was assessed using a self-reported questionnaire.
Results: 29.3% of men and 25.0% of women were smokers. Prevalence of obesity, abdominal obesity, and excess of BF was 16.9% and 26.6% and 14.2% in men and 15.0%, 33.0% and 27.5% in women, respectively. Smokers had lower age-adjusted mean WC and percent of BF compared to non-smokers. However, among smokers, mean age-adjusted WC and BF increased with the number of cigarettes smoked per day: among light (1–10 cig/day), moderate (11–20) and heavy smokers (>20), mean ± SE %BF was 22.4 ± 0.3, 23.1 ± 0.3 and 23.5 ± 0.4 for men, and 31.9 ± 0.3, 32.6 ± 0.3 and 32.9 ± 0.4 for women, respectively. Mean WC was 92.9 ± 0.6, 94.0 ± 0.5 and 96.0 ± 0.6 cm for men, and 80.2 ± 0.5, 81.3 ± 0.5 and 83.3 ± 0.7 for women, respectively. Compared with light smokers, the age-adjusted odds ratio (95% Confidence Interval) for excess of BF was 1.04 (0.58 to 1.85) for moderate smokers and 1.06 (0.57 to 1.99) for heavy smokers in men (p-trend = 0.9), and 1.35 (0.92 to 1.99) and 2.26 (1.38 to 3.72), respectively, in women (p-trend = 0.04). Odds ratio for abdominal obesity vs. normal WC was 1.32 (0.81 to 2.15) for moderate smokers and 1.95 (1.16 to 3.27) for heavy smokers in men (p-trend <0.01), and 1.15 (0.79 to 1.69) and 2.36 (1.41 to 3.93) in women (p-trend = 0.03).
Conclusion: WC and BF were positively and dose-dependently associated with the number of cigarettes smoked per day in women, whereas only WC was dose dependently and significantly associated with the amount of cigarettes smoked per day in men. This suggests that heavy smokers, especially women, are more likely to have an excess of BF and to accumulate BF in the abdomen compared to lighter smokers.

P15

Impact of smoking and quitting on adipose tissue metabolism in smokers

Gonseth S., Willi C., Bize R., Cornuz J. (Lausanne)

Background: Weight gain following cessation is a frequent reason argued by smokers to continue to smoke or to relapse. Some metabolic parameters might mediate or modulate weight gain. Our objective was to explore the evolution of three metabolic parameters such as leptin and insulin among sedentary adults smokers who participated to a randomized controlled trial assessing moderate-intensity physical activity (PA) as an aid for smoking cessation. Whereas the primary outcome, i.e. continuous smoking abstinence, was similar in both groups at one-year follow-up, we performed secondary analyses to estimate impact of smoking and quitting on adipose tissue metabolism in smokers.
Methods: 481 participants divided in two groups attended a 9-week program with a weekly 15-min. smoking cessation intervention (counseling and prescription of NRT). The intervention group attended a 60-min. moderate-intensity PA program, whereas the control group attended 60-min. health education program to ensure equal contact conditions. A visit was scheduled at 12th week and at 6 and 12 months follow-up. Blood fasting serum insulin and leptin levels were assessed.
Results: There were no age, smoking habits, socio-demographic data and metabolic parameters baseline differences between the two groups (leptin: 8.6 and 10.1 mg/l, insulin: 10.6 and 11.4 mU/l, in control and intervention groups respectively, all p values NS). The mean body weight gain from baseline to week 52 was 3.6 kg and 2.9 kg for control and intervention groups respectively (p = 0.11). The intervention group performed a higher weekly volume of PA than the control group (e. g., at week 12: 2285.6 METS *min/ week vs. 1746.7 METS*min/week, p <0.05). At week 52, more participants achieved PA recommendations in intervention vs. control groups (77.8% vs. 60.3%, p = 0.005). Leptin level increased among participants of both groups between the first visit and visits at weeks 12, 24 and 52, and this increase was greater in control than in intervention groups: +2.4 vs. +1.8 mg/l at week 12 (p = 0.6), +3.2 vs. +1.7 mg/l at week 24, (p = 0.03), + 3.2 vs. +1.2 mg/l at week 52 (p = 0.05). The p values of the trend test were NS. Insulin level also tended to increase among participants during follow-up (control vs. intervention values): +0.4 vs. +0.4 mU/l at week 12, +0.7 vs. +0.8 mU/l at week 24, + 2.4 vs. +1.8 mU/l at week 52 (all p values NS). The trend tests were significant for control (p = 0.01) and borderline for intervention groups (p = 0.07).
Conclusion: Leptin level increased after smoking cessation and this increase was greater among smokers of the control group who practiced lower weekly volume of PA. Leptin might be a potential causal factor explaining weight gain following smoking cessation. Insulin level showed a statistically significant increase only among smokers of the control group. Insulin may also be involved in weight gain following smoking cessation.

P16

Verbesserung vaskulärer Risikofaktoren nach Adipositas-Behandlung mittels bariatrischer Chirurgie

Wieland T., Villiger P., Reinhart W.H. (Chur)

Die Adipositas stellt in unserer Gesellschaft ein wichtiges und zunehmendes Problem dar. Sie ist mit einer erhöhten kardiovaskulären Morbidität und Mortalität vergesellschaftet. Mit der bariatrischen Chirurgie besteht heute die Möglichkeit einer effizienten Behandlung bei einem Body Mass Index (BMI) >40 kg/m^2. Damit kommt es zur Verbesserung von kardiovaskulären Risikofaktoren und zu einer Abnahme an vaskulären Todesfällen. Wir haben an unserem Kollektiv von 20 PatientInnen (18 Frauen, 2 Männer, Alter 42 ± 8 Jahre) ein Jahr nach bariatrischem Eingriff kardiovaskuläre Risikofaktoren untersucht. 19 hatten eine Operation nach Sugerman (Magenverkleinerung, Gastrojejunostomie und Anastomisierung des proximalen Jejunums mit dem distalen Ileum), eine Patientin ein Gastric banding erhalten. Der BMI betrug vor der Operation 46,5 ± 6,5. Innerhalb eines Jahres nahmen die PatientInnen 42 ± 13 kg ab, was den BMI auf 31,3 ± 6,3 senkte (p <0,0001). Der BD sank systolisch von 137 ± 13 auf 128 ± 12 mm Hg (p <0,02), diastolisch von 82 ± 8 auf 77 ± 10 mm Hg (p <0,05). Das C-reaktive Protein (CRP) sank von 8,4 ± 6,7 auf 1,6 ± 2,3 mg/l (p <0,0001, n = 18). Das Gesamt-Cholesterin fiel von 4,93 ± 0,71 auf 4,00 ± 0,71 mmol/l (p <0,01, n = 14).
In einer Untergruppe von acht Patienten wurden auch LDL und HDL gemessen und ein tendentieller Abfall von LDL von 3,59 ± 0,62 auf 2,56 ± 0,05 mmol/l und ein Anstieg von HDL von 1,29 ± 0,34 auf 1,39 ± 0,31 mmol/l (n.s.) gefunden. Die Harnsäure sank von 373 ± 137 auf 285 ± 77 µmol/l (p <0,01, n = 11).
Wir schliessen aus diesen Daten, dass bariatrisch-chirurgisch behandelte PatientInnen mit einer morbiden Adipositas ein Jahr nach Eingriff ein deutlich verbessertes kardiovaskuläres Risikoprofil aufweisen. Das Absinken des CRP ist eine neue Beobachtung, welche darauf hindeuten könnte, dass das Fettgewebe eine systemische entzündliche Reaktion unterhalten kann.

P17

Spleen derived vascular progenitor cell transfer restores metabolic and vascular insulin sensitivity in high-fat diet insulin resistant mice

Bloch J., Schwab M., Duplain H., Dessen P., Monney A., Mathieu C., Sartori C., Scherrer U. (Lausanne)

Type 2 diabetes, insulin resistance and its associated cardiovascular complications are reaching epidemic proportions worldwide, but the underlying mechanisms remain incompletely understood. Endothelial dysfunction related to defective NO synthesis contributes to metabolic insulin resistance by leading to impaired insulin stimulation of blood flow and substrate delivery to skeletal muscle tissue. Circulating endothelial progenitor cells (EPC) play a role in endothelial repair and function, and represent a marker of endothelial dysfunction Administration of functional EPC restores this defect. Diabetes and insulin resistance are associated with a decreased number and dysfunctional EPC, but it is not clear whether this is a cause or merely a consequence of the disease. We hypothesized that transfer of functional EPC improves insulin sensitivity in insulin resistant mice. Six weeks old splenectomized C57/Bl6 mice were put on a high-fat diet (UAR, France) for 8 weeks. 4 and 6 weeks after the start of the diet, mice received an i.v. injection of 200 Mio vascular progenitor cells in normal saline, or vehicle. The cells were prepared by extracting the monocytic fraction from spleens of C57/Bl6 mice. 2 weeks after the

second injection, we assessed insulin sensitivity (intraperitoneal insulin injection, 0.5 U/kg). We also measured insulin stimulation of muscle blood flow in vivo, and skeletal muscle glucose uptake in vitro. The major new findings were that EPC transfer markedly improved both metabolic and vascular insulin sensitivity in insulin-resistant mice. The decrease in basal glycemia 15 min after insulin injection was more than twice as large in EPC-treated than in vehicle-treated mice (–26.1 ± 3.0% vs. –10.8 ± 4.2%, P = 0.012). The insulin-induced stimulation of skeletal muscle blood flow in vivo was more than 4 times larger in the EPC-treated than in the control mice (95.4 ± 22.1% vs. 22.4 ± 9.7% P <0.01), whereas the basal and insulin stimulated glucose uptake in isolated muscle in vitro was similar in the two groups (P = 0.97). Here we show for the very first time that heterologous transfer of circulating vascular progenitor cells markedly improves insulin sensitivity in insulin resistant mice. This favorable metabolic effect appears to be related, at least in part, to restoration of the endothelium-dependent vasodilation insulin stimulation of blood flow and substrate delivery in skeletal muscle tissue.

P18

An unusual case of hyperammonemia and coma without liver dysfunction

Ritter S., Senn A., Isler P., Meier C.A., Frick S. (Zurich)

Background: Ammonia is a neurotoxin mainly produced in the gastrointestinal tract and cleared almost completely from the portal vein by the liver. Hence, hepatic encephalopathy due to hyperammonemia typically occurs in patients with advanced liver disease and impaired ammonia clearance.
Case: A 65-year old comatose patient (GCS score 4) with a bilateral positive Babinski sign had to be intubated for airway protection. Because of a depressive mood disorder she had been treated with haloperidol and valproic acid (Depakine® 300 mg daily). Head CT scan and analysis of cerebrospinal fluid were both normal. EEG showed a deep coma curve without evidence of epileptic activity. Laboratory test revealed a normal blood glucose and normal liver function, except for an increased INR under therapy with oral anticoagulation. Toxicology screening was negative. All medication was then stopped including valproic acid (serum level 176 micromol/L; therapeutic range 340–690). One day after admission, serum ammonia level was found to be elevated at 69 micromol/L (normal range 11–32). Without further interventions the patient became conscious and was successfully extubated. EEG showed considerable improvement. The ammonia level decreased gradually within the next few days following withdrawal of valproate. Thus, the diagnosis of valproate-related hyperammonemic encephalopathy was made.
Discussion: After acute overdose or chronic use of valproic acid (VPA; 2-propylpentanoic acid) hyperammonemia may occur, but is not always accompanied by liver dysfunction. Propionic acid, a metabolite of VPA, inhibits mitochondrial carbamyl phosphate synthetase which is necessary for ammonia elimination via the urea cycle. If the action of this enzyme is impaired, ammonia accumulates and may lead to encephalopathy. VPA may also raise ammonia levels through an interaction with carnitine. Serum ammonia concentrations actually inversely correlate with serum levels of carnitine. In addition to the discontinuation of VPA, therapy with carnitine could possibly be a therapeutic option in suspected metabolic encephalopathy.
Conclusion: Symptomatic hyperammonemia with severe neurological impairment may occur under therapy with valproic acid (Depakine®, Orfiril®, Convulex®) without abnormalities of liver function tests. When valproate-related hyperammonemic encephalopathy is suspected, the drug must be stopped immediately. This condition is rare and usually reversible when valproate is discontinued.

P19

Das Berner Modell: Resultate der Integrativen Adipositasbetreuung 2003 bis 2007

Egermann U., Cottagnoud P., Laederach-Hofmann K. (Bern)

Als Epidemie des 21. Jahrhunderts stellt die Adipositas eine zunehmende medizinische Herausforderung dar. Auch in ökonomischer Hinsicht kommen durch die resultierenden kardiovaskulären, neoplastischen, degenerativen und psychiatrischen Folgeerkrankungen erhebliche Mehrbelastungen auf das öffentliche Gesundheitswesen zu. Zahlreiche verschiedene Interventionen weisen teils eindrückliche Anfangserfolge hinsichtlich der Gewichtsreduktion auf, lassen aber eine Nachhaltigkeit und vor allem einen Effekt auf die kardiovaskulären Erkrankungen vermissen. Aus diesem Grund wird in dem seit 2003 etablierten «Berner Modell» ein interdisziplinäres Therapiekonzept für adipöse Patienten mit einem BMI >30 kg/m^2 verfolgt. Neben einer Gruppentherapie wird auch eine Einzeltherapie bestehend aus internistischer, psychosomatischer, ernährungstherapeutischer und physiotherapeutischer Betreuung angeboten. Gegebenenfalls erfolgt eine adjuvante medikamentöse Therapie. Zusätzlich zu Bewegungstherapie und Körperwahrnehmungsschulung kommen verhaltenstherapeutische Ansätze bei Essstörungen zum Einsatz. Dem präventiven Aspekt wird durch Einbezug von Angehörigen und Unterstützung für Selbsthilfegruppen von Patienten Rechnung getragen. Aktuell nehmen über 700 Patienten am Programm teil. Davon konnten im Jahr 2007 die ersten 113 Patienten das 3jährige ambulante Programm abschliessen. Die 35 Patienten des Gruppenprogramms erreichten eine nichtsignifikant grössere Gewichtsabnahme verglichen mit 78 Patienten aus dem Einzelprogramm. Demographisch unterscheiden sich weder die Patienten des Gruppen- oder Einzelprogrammes, noch die ausgeschiedenen Patienten: 76% der Patienten sind weiblich. Das Alter reicht von 25 bis 75 Jahren (Mittelwert 46 Jahre). Der Median liegt bei 48 Jahren. Die vergleichsweise hohe Anzahl von 130 Patienten, die in den ersten 3 Jahren aus dem Programm ausgeschieden sind, setzt sich zusammen aus Gruppenwechseln, Weiterbetreuung in einem wohnortnäheren Zentrum, Einleitung einer bariatrischen Therapie und drop-outs. Im Verlauf des Jahres 2008 werden erste Aussagen zur Beeinflussung des kardiovaskulären Risikoprofils möglich sein.

P20

Patients under Scrutiny for Renal Function point to Holotranscobalamin (HoloTc; active B12) rather than Methyl Malonic Acid (MMA) to elucidate Vitamin B12 Deficiency

Risch L., Zerlauth M., Risch M., Bernasconi L., Flahaut F., Weber M., Risch G., Michel-Blanco M., Nydegger U. (Liebefeld, Schaan, Pregassona)

Cobalamin, i.e. Vitamin B12 governs DNA synthesis, deficient states resulting in megaloblastic nuclear-cytoplasmic asynchrony. Quantitative estimations of holotranscobalamin (HoloTc, the biologically active fraction of vitamin B12) and MMA (a protein breakdown-metabolite) are frequently used in early diagnosis of vitamin B12 deficiency but the predictive value of the latter remains a matter of debate. It has been suggested that renal insufficiency may cause elevation of MMA. The present study was designed to estimate the relative importance of HoloTc and MMA as markers for early stages of vitamin B12 deficiency in a homogenous study population under scrutiny for kidney function. Vitamin B12 status of adults was evaluated using the UniCel® Beckman Coulter (Nyon), HoloTc was was measured using the Axsym Abbott Diagnostics (Baar) and MMA was measured by gaschromatography/massspectrometry. A modified kinetic Jaffe method available on a Cobas Integra (Roche Diagnostics, Rotkreuz) for creatinine level measurements was used to estimate kidney function; the glomerular filtration rate (GFR) was calculated using the abbreviated, simplified equation to predict GFR (Modification of Diet in Renal Disease Study Group, MDRD). The 232 patients (59.9% female; mean age 57 + 17 years) expressed a mean concentration of vitamin B12 of 277 pmol/L, 50 pmol/L of holoTc and 197 nmol/L MMA, considering levels of B12 <125 pmol/L, holoTc <35 pmol/L or MMA >271/L to indicate clinically relevant vitamin B12 deficiency. Correlating GFR (eGFR 30–60 ml/min/1.73m^2: 8.2%; eGFR 60–90 ml/min/1.73m^2: 34.5%) to the markers of Vitamin B12 deficiency revealed a significant association between kidney function and MMA ($r = 0.31$, $p < 0.001$), whereas no such association could be seen between kidney function and concentrations of total vitamin B12 and HoloTc. Vitamin B12 deficiency and chronic kidney disease are frequent conditions among elderly patients. Our study in a rather homogenous study population under investigation for kidney function lends further support to the view that holoTc measurements rather than MMA direct the way to meaningful diagnosis of vitamin B12 deficiency.

P21

Acrocyanosis: an unusual manifestation of pheochromocytoma

Weiss L., Schleyerbach P., Rutishauser J., Glück Z. (Biel)

A 44 year-old male was referred by his family physician because of newly diagnosed hypertension detected during routine examination. Blood pressure had been as high as 247/114 mm Hg. The patient gave a history of headaches for the past year and diaphoresis for the past six months. He reported no palpitations. For around 6 months prior to referral, he had experienced Raynaud's phenomenon on his fingers, and for a few days he had noticed bluish discoloration of his nose, elbows, knuckles, and ankles. Apart from episodes of low back pain, his past medical history was uneventful. Upon referral, the patient was sweating, blood pressure was 174/117 mm Hg, and the heart rate was regular at 79/min. The rest of the cardiovascular physical examination was normal. His nose, knees, elbows, finger tips, and toes were cyanotic and cool. The lesions were not palpable and nontender. Laboratory analysis revealed massively elevated plasma levels of free normetanephrine 12760 pM (reference range: 120–917), whereas the level of plasma free metanephrine was normal at 120 pM (reference range: 61-608). A biochemical diagnosis of pheochromoyctoma was made. Upon MRI, a 5 cm left adrenal mass was identified. The patient was instructed to keep a salt-rich diet and started on phenoxybenzamine in increasing doses for 14 days. Under this therapy, the skin lesions started to regress. The mass was succefully removed by laparoscopic adrenalectomy. Histologic workup confirmed a pheochromocytoma. Postoperatively, the patient's blood pressure returned to normal, and the acrocyanosis disappeared within 7 days. The skin manifestations observed in our patient are not commonly associated with pheochromocytoma. Most likely, they were caused by arteriolar vasoconstriction due to the (alpha) – sympathomimetic effect resulting from the isolated production of large amounts of norepinephrin by the tumor.

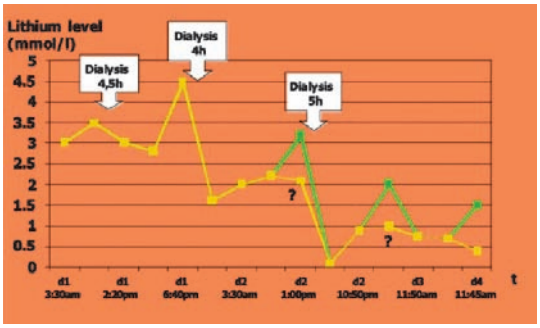
P22

Pseudohyperlithiemia

Meyer-Heim T., Gerber L., Hanhart A., Heuss L.T., Bleisch J.A. (Zollikerberg)

Background: Therapy of lithium intoxication not only relies on clinical assessment but also on drug levels. Incorrect sampling methods can lead to falsely elevated values.

Case study: A 41-year-old female patient with a history of depression and multiple suicide attempts was admitted to our emergency department after deliberate ingestion of 60 to 80 pills of Lithiofor®, containing 12 mmol lithium each. Initial therapy comprised intravenous rehydration and administration of purgatives. The patient was intubated due to vomiting and mechanical ventilation was started. An emergency haemodialysis session was begun after the lithium level had reached 3.5 mmol/l. The lithium level dropped to 3.0 mmol/l after 4.5 h of intermittent haemodialysis. Due to rebounds (levels reaching 4.5 mmol/l, 3.2 mmol/l respectively), a second and third dialysis session were mandatory. As we found out later, three of the analysed samples were taken from test tubes containing lithium-heparin, elevating the lithium level artificially. A falsely elevated lithium level had led to an unnecessary third haemodialysis session.
Discussion: The correct sampling of lithium levels in patients with suspected lithium intoxication is crucial. Heparin test tubes (green) contain lithium-heparin and therefore indicate falsely elevated lithium levels. In our case, one dialysis session was performed because of an incorrectly measured high drug level due to a sampling error. Presence of lithium-heparin can lead to remarkable differences in lithium level results and hence to unnecessary, potentially dangerous therapeutic procedures. The difference is estimated to lie between 0.88 mmol/l (reference value) and 1.5 mmol/l (literature). In our case the difference amounted to 1.1 mmol/l.
Figure 1: Lithium level



P23

Decreased kidney function and the coronary angiographic state independently predict future vascular events

Risch L., Saely C.H., Rein P., Hoefle G., Gouya G., Aczel S., Vonbank A., Drexel H. (Feldkirch & Liebefeld, Feldkirch & Triesen, Hohenems, Feldkirch)

Background: Despite the fact that impaired kidney function represents a cardiovascular risk factor, data on the relationship between kidney function markers, angiographic state and future cardiovascular events in coronary patients are scarce.
Aims: To investigate the relationship between kidney function and the presence of coronary artery disease. In addition, we wanted to investigate the relationship between several markers of kidney function and the occurrence of cardiovascular events.
Methods: We investigated 195 consecutive patients (age 63+/-10 years; 30.3% female) undergoing coronary angiography for the evaluation of stable coronary artery disease (CAD) and assessed kidney function by means of several markers (cystatin C, cysC / beta-2–microglobulin, B2M / beta-trace protein, BTP, all measured with PENIA on Prospec, Dade-Behring; urea, Ur / creatinine, Cr, photometric measurements with Roche reagents on Hitachi 717 or 911; eGFR calculated with MDRD and Mayo Clinic Quadratic, MCQE, equations). All patients had kidney function tests performed on samples taken right before coronary angiography. Prospectively, we recorded major coronary events and cumulative vascular events over 6 years.
Results: 61.5% of the patients had significant coronary stenoses with a lumen narrowing >/ = 50%. With the exception of Cr ($p = 0.002$), there were no significant differences among the different kidney function markers between patients with CAD and those in whom angiography did not show CAD. In logistic regression adjusting for age, sex, BMI, the presence of diabetes mellitus, smoking, hypertension, CRP, LDL & HDL, none of the investigated kidney function parameters was associated with significant coronary stenoses. Prospectively, the risk of future vascular events, as assessed by Cox regression analysis was significantly increased with CysC,B2M, UR, and Cr-based methods, independently from coronary angiographic status ($p < 0.05$ for all).
Conclusions: In coronary patients, there is no relationship between the investigated kidney function markers and coronary status. Prospectively, however, CysC, B2M, UR, and creatinine-based methods for estimation of GFR independently from coronary angiographic status predict future vascular events.

P24

Fibrosing colonopathy – Late-onset gastrointestinal complication of cystic fibrosis?

Franzen D., Went P., Bühlmann U. (Zollikerberg, Zürich)

Cystic fibrosis is an autosomal recessive disease affecting exocrine glands of the respiratory and gastrointestinal system. Cystic fibrosis is associated with several serious complications in the lower intestinal tract including rectal prolapse, distal intestinal obstruction syndrome (DIOS), intussusception, Crohn's disease, carcinoma, volvulus, (silent) appendicitis, and fibrosing colonopathy (FC). It seems to be confirmed, that high-strength or even low-strength pancreatic enzymes are the leading cause of FC. The large majority of the published patients were children receiving pancreatic enzymes. The incidence of FC in adults is much lower, and the pathogenesis is – analogous to paediatric patients – typically associated with the use of pancreatic enzyme substitution in patients with cystic fibrosis. But, patients with enzyme substitution because of other reasons than cystic fibrosis have not been associated with FC. We present a case of a 43 years old female cystic fibrosis patient suffering from FC, who had never been exposed to pancreatic enzyme supplementation. This case emphasizes that FC also occurs in absence of pancreatic enzyme substitution and pancreas insufficiency. It could therefore be considered a late-onset gastrointestinal complication of cystic fibrosis in its natural course of disease. Consequently, the age could be a risk factor for the appearance of FC in all patients with cystic fibrosis.

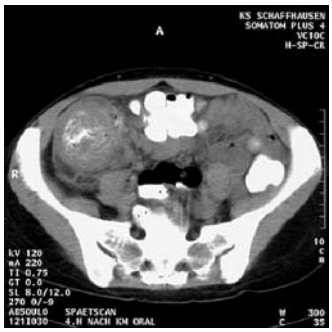


Figure 1
CT scan abdomen

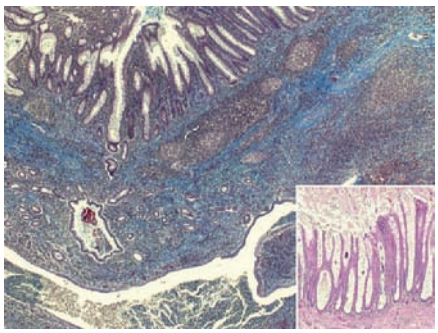


Figure 2
Histopathology

P25

Case report: splanchnic arteriovenous malformation as a cause of protein loosing enteropathy

Pasche A., Cosma-Rochat M., Doerig C., Moradpour D., Qanadli S., Vollenweider P. (Lausanne)

Introduction: Arteriovenous malformations (AVM) constitute a rare cause of upper gastrointestinal (GI) bleeding. AVM can also induce functional portal hypertension and, secondarily, stasis within lympathic vessels of the intestinal wall leading to protein loosing enteropathy (PLE).
Case report: A 61-year-old man with a longstanding PLE of unknown origin, without chronic hepatic disease, was admitted for massive upper GI hemorrhage. Endoscopy revealed large varices of the gastric fundus with difficult-to-control acute bleeding. Selective arteriography showed active bleeding from an extensive AVM located in the gastric wall. Repeated selective embolizations of the left gastric and splenic arteries feeding the AVM allowed to control the hemorrhage. Transhepathic portography performed after the embolizations documented the absence of portal hypertension. The clinical condition of the patient improved and there was no recurrence of GI bleeding. The patient was able to eat again normally and gained 7 kg within 7 weeks following hospital discharge. Common causes of PLE, including celiac disease, Crohn's disease and ulcerative colitis, were excluded. The macroscopic appearance of the duodenum and the proximal small bowel was compatible with lymphangiectasia.
Interpretation: AVM of the left gastric and splenic arteries induced a massive increase in blood flow to the portal system which resulted in portal hypertension. This may have caused venous and lymphatic stasis of the small intestine, resulting in PLE. Correction of the shunt and portal hypertension should lead to the reversal of the PLE in this patient. Short-term follow-up seems to confirm this hypothesis but we will carefully monitor this patient for long-term weight gain and correction of iron, vitamin and protein deficiencies.

P26

Viscosity of human bile from the common bile duct sampled during endoscopic retrograde cholangiography

Näf G., Werth B., Reinhart W.H. (Chur)

Background: Bile flow is determined by its viscosity. While hepatic bile has a low viscosity (slightly higher than water), water reabsorption and mucin secretion leads to a several-fold higher bile viscosity in the gallbladder. We measured the viscosity of bile from the common bile duct during endoscopic retrograde cholangiography (ERC).
Methods: In patients undergoing ERC for various clinical reasons, bile was aspirated immediately after cannulation of the papilla vateri. The samples were deep-frozen at –80°C and later thawed prior to viscosity measurements at 37°C. A Couette-type viscometer (Contraves LS30) was used with a broad range of shear rates (0.08–69.5 s^{-1}). If not stated otherwise, the value at the shear rate of 0.95 s^{-1} was taken into account.
Results: Bile from the common bile duct of 138 patients was measured. The majority (64.5%) had bile viscosities between water (0.7 mPa.s) and the lower limit of plasma (1.1 mPa.s). At these low viscosities, bile showed a Newtonian behaviour, i.e. the viscosity was independent of the shear rate. 20 patients (14.5%) had a bile viscosity above that of plasma (>1.4 mPa.s). These bile samples showed a Non-Newtonian behaviour, i.e. the viscosity increased exponentially with decreasing shear rate. Cholecystectomized patients had a lower bile viscosity, which is explained by the absence of viscous bile from the gallbladder. Bile viscosity was similar in patient groups with either choledocholithiasis, sludge, cholangitis, biliary pancreatitis, or carcinoma of the pancreas or cholangiocarcinomas.
Discussion and conclusions: Bile viscosity in the common bile duct is lower than that of plasma in 65% of patients undergoing ERC. In 15% it is higher than plasma viscosity, which is caused by the mucin content of bile. Such viscous bile is a Non-Newtonian fluid, i.e. its viscosity increases exponentially with decreasing flow rate, which may lead to a vicious cycle in cholestasis. Bile viscosity showed a large variation independent of the underlying disease.

P27

Hyperferritinämie-Katarakt-Syndrom

Pohl D., Tutuian R., Baechli E., Gubler C. (Uster, Zürich)

Fallbeschreibung: Ein 32jähriger Patient stellte sich bei chronischer Müdigkeit beim Hausarzt vor. Im Blut imponierte eine Hyperferritinämie (1314 µg/l) bei normaler Transferrinsättigung (23,3%), woraufhin die Zuweisung zur Leberbiopsie erfolgte. In der Anamnese kein Anhalt für eine Hepatopathie; Noxen, insbesondere Alkoholabusus werden verneint. Weiterhin ergaben sich keine Hinweise für einen M. Gaucher, M. Still, eine Hyperthyreose oder eine Hämophagozytose. Die Transaminasen waren normal; eine Genetik betreffend Hämochromatose (HFE) zeigte eine Heterozygotie für H63D, was eine HFE unwahrscheinlich macht. Die Histologie zeigte einen Normalbefund; eine Eisentrockengewichts-Bestimmung konnte wegen ungenügender Materialmenge nicht durchgeführt werden. Aufgrund einer Hyperferritinämie ohne hepatische Eisenüberladung wurde nach einem Katarakt gefragt: Der Patient leidet seit früher Kindheit an einem beidseitigem Katarakt (Abb. 1); die daraufhin erhobene Familienanamnese zeigt Abb. 2.
Hintergrund und Diskussion: Das hereditäre Hyperferritinämie-Katarakt Syndrom ist eine seltene autosomal-dominante Erkrankung, die oft als hereditäre Hämochromatose misdiagnostiziert wird. Sie ist durch erhöhte Serumferritinwerte bei normaler Transferrinsättigung in der Abwesenheit hepatischer Eisenüberladung charakterisiert und führt bereits in jungem Alter zur okulären Kataraktbildung. Andere Organmanifestationen insbesondere Hepatopathien oder Symptome sind nicht bekannt. Die Linsentrübungen entstehen laut aktueller Literatur auf dem Boden einer Akkumulation von Ferritin-Leichtketten (LFT) respektive Ihrer Metaboliten. Die genetisch verantwortliche Region liegt um die 5'UTR-Region des Gens, welches für Ferritin-Leichtketten kodiert und kann multipel verändert sein. Die genetische Diagnostik des aktuell vorgestellten Patienten ist noch ausstehend. Nach Ausschluss einer sekundären Hyperferritinämie sollte mittels Bestimmung der Transferrinsättigung und ggfs. einer Leberbiopsie eine hepatische Eisenüberladung gesucht werden. Nach Ausschluss derselben sollte differentialdiagnostisch eine Acoeruloplasminämie respektive das beschriebene Syndrom mit juvenilem Katarakt in Betracht gezogen werden.

Abb. 1
Beispiel eines Linsenkatarakts

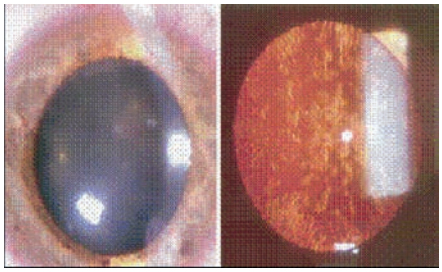
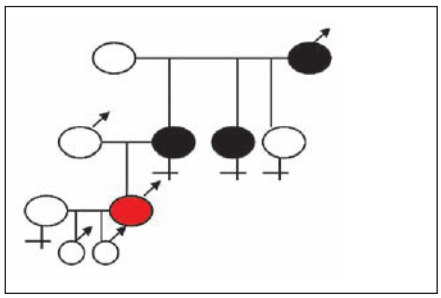


Abb. 2
Familienstammbaum, rot kennzeichnet Patient, schwarz weitere Katarakt-Träger



P28

Indikationen zur Detektion und Charakterisierung fokaler Leberläsionen mittels Kontrastmittelsonographie – eine retrospektive Analyse von 158 Untersuchungen

Schiemann U., Tshering D., Kunz A., Patak MA., Stickel F., Szuecs Z. (Bern)

Hintergrund: Die Sonographie mit Echosignalverstärkern (Kontrastmitteln) hat das Potential, die Detektionsrate und die Charakterisierung von fokalen Leberläsionen deutlich zu verbessern. Ziel unserer Studie war die deskriptive Erfassung der Indikationen zu kontrastmittelsonographischen Untersuchungen und die Dokumentation der entsprechenden Befunde.
Methode: In einer retrospektiven Analyse wurden die Daten von Kontrastmittelsonographien der Leber (Siemens Sequoia, SonoVue fraktioniert 5 ml intravenös) bei 158 Patienten (Durchschnittsalter 55 Jahre +/- 14,5 SD) zu ihren Indikationen und den Befunden ausgewertet. Die Indikationen für die Kontrastmittel-Sonographie waren im Einzelnen: a) B-Bild-sonographisch nachgewiesene Läsion (n = 30), b) abklärungsbedürftige Läsion als Zufallsbefund im CT oder MR (n = 18), c) Patienten mit Malignom-oder Metastasenverdacht (n = 30) und d) Routineuntersuchung von Patienten mit einer Leberzirrhose oder Status nach Lebertransplantation (HCC-Screening) (n = 80).
Ergebnisse: Basierend auf der B-Bild-Sonographie und der Kontrastmitteldynamik liessen sich mit hoher diagnostischer Sicherheit nachweisen: 39 Hämangiome, 4 Adenome, 2 fokal noduläre Hyperplasien (FNH), 19 fokale Minder- oder Mehrverfettungen, 8 Regeneratknoten bei Leberzirrhose, 2 Abszesse, 2 unkomplizierte Zysten, 9 Fälle mit Lebermetastasen und 12 HCC. Von letzteren wurden 9 durch Screening von Patienten mit Leberzirrhose detektiert. In 61 Fällen konnte eine fokale Leberläsion ausgeschlossen werden.
Schlussfolgerung: Die Kontrastmittelsonographie ist eine preiswerte und nebenwirkungsarme Untersuchungsmethode zur Charakterisierung von bildgebend nachgewiesenen Leberläsionen sowie zur Metastasensuche. Ein systematisches Screening von Patienten mit Leberzirrhose führte in immerhin 11% zum Nachweis einer HCC-verdächtigen Läsion.

P29

Physician speciality and pain reduction in patients with depressive symptoms under treatment with venlafaxine

Begré S., Traber M., Gerber M., von Känel R. (Bern, Zug, Unterägeri)

Excessive pain perception may lead to unnecessary diagnostic testing or invasive procedures to result in iatrogenic complications and prolonged disability. Naturalistic studies on depressed patients with chronic pain investigating the impact of medical speciality on treatment outcome in a primary care setting are lacking. Venlafaxine and other antidepressants may alleviate pain in depressed patients. In this observational study, we examined whether the magnitude of pain reduction in 444 depressed patients under venlafaxine would differently relate to the medical speciality of the 122 treating physicians, namely psychiatrists (n = 110 patients), general practitioners (n = 236 patients), and internists (n = 98 patients). Independent of demographic factors, comorbidity, severity of pain and illness at study entry, and the duration of pain and depression, patients seemed to profit significantly less in terms of pain reduction ($p < .001$) and of reduction in severity of their illness by psychiatrists as compared to general practitioners ($p < .019$) and internists ($p < .002$). The findings suggest that patients referred to psychiatrists are more difficult to treat than those referred to general practitioners and internists. Therefore, psychiatrists could particularly profit from educational programs targeting at improving their capacities in treating pain of their depressed patients.

P30

Physical pain in patients with depressive symptoms in switzerland: a field report from clincal practice

Begré S., Traber M., Gerber M., von Känel R. (Bern, Zug, Unterägeri)

The present study is a cross-sectional observation of 601 depressed pain patients from all over Switzerland who were treated with Venlafaxin in 122 medical practices. Pre-existing or other additional, antidepressant medication was not taken into account. Diagnosis of depression was determined by a regular clinical interview, pain intensity was estimated using a visual analogue scale (VAS), and severity of disease was rated by the Clinical Global Impression scale (CGI). Age, gender, duration of depression, and all clinically approved diagnoses for comorbid somatic and mental disorders (i.e. the first digit according to ICD-10) were listed. The use of opioid and non-opioid analgesics and the number of therapies in addition to those targeting depression and pain were also recorded. Compared with Central European patients, those from the Balkans and Southern Europe appear to present with more intense, overall pain mainly affecting the head, extremities and back, whereas Southern Europeans tend to suffer even more frequently from chest pain compared with their Central European peers. There is no difference in terms of pain intensity between patients from the Balkans and those from Southern Europe.

P31

Pour une plus grande place de l'enseignement de santé communautaire dans les cursus de médecine clinique

Motamed S., Rougemont A. (Genève)

Les déterminants sociaux de la santé ont une importance majeure sur l'état de santé de notre population. Pourtant, les objectifs d'enseignements en médecine sociale et préventive sont, de notre avis, encore trop peu représentés dans les programmes d'enseignements postgradués de médecine interne et de médecine générale. De plus, les médecins déjà formés et pratiquant en cabinet sont peu exposés à cette problématique dans les offres de formation continue, en raison d'un cloisonnement trop important entre médecine clinique et santé publique. Pourtant, l'évolution des besoins de notre population devrait imposer de revoir à la fois la part des financements dévolus aux différents déterminants de la santé, ainsi que le profil des différents professionnels de santé. Dans cette dernière tâche en particulier, le rôle de l'Université est majeur et devrait fortement se concrétiser dans l'interaction que devraient avoir les Instituts de Médecine Sociale et Préventive chargés de l'enseignement de la santé publique dans les Facultés et les Hôpitaux universitaires, incontournables pour l'obtention d'un FMH et de plus en plus impliqués dans la formation continue. Différentes formes de collaborations sont discutées, ainsi que les possibilités très concrètes de rotations au sein des Instituts pour des médecins praticiens désirant s'investir dans des problématiques communautaires.

P32

Clinical supervisors' perceived needs for teaching communication skills in clinical practice

Junod Perron N., Sommer J., Hudelson P., Demaurex F., Luthy C., Nendaz M., Dolmans D., Van der Vleuten C., de Grave W. (Geneva, Maastricht)

Background: Lack of faculty training is often cited as the main obstacle to post-graduate teaching in communication skills.
Objectives: To explore clinical supervisors' needs and perceptions regarding their role as communication skills trainers.
Methods: Four focus group discussions were conducted with clinical supervisors from two inpatient and one outpatient medical services from the Geneva University Hospitals. Focus groups were audio taped, transcribed verbatim and analyzed in a thematic way using Winmax software for qualitative data analysis.
Results: Clinical supervisors said they frequently addressed communication issues with residents but tended to intervene as rescuers, clinicians or coaches rather than as formal instructors. They felt their own training did not prepare them to teach communication skills. Other barriers to communication skills teaching include lack of time, competing demands, lack of interest and experience on the part of residents, and lack of institutional priority given to communication issues. Respondents expressed a desire for experiential and reflective training in a work-based setting and emphasized the need of a non judgmental learning atmosphere.
Conclusions: Results suggest that organisational priorities, culture and climate strongly influence the degree to which clinical supervisors may feel comfortable to teach communication skills to residents. Attention must be given to these contextual factors in the development of an effective communication skills teaching program for clinical supervisors.

P33

Wieviel Salz enthält ein Nahrungsmittel oder die Unverständlichkeit der Lebensmittelettiketierung

Käppeli S., Cajacob A., Brändli O., Suter P.M. (Zürich)

Hintergrund: Verschiedene Ernährungsfaktoren sind in der Pathogenese und Therapie der chronischen Erkrankungen von zentraler Bedeutung. Salz (NaCl) kann beim vorliegen einer Salzsensitivität zum Bluthochdruck beitragen. Die Kenntnis des Salzgehaltes von Nahrungsmitteln ist für den Konsumenten von zentraler Bedeutung. In dieser Studie wurde das Ernährungswissen respektive die Kenntnisse über den Salzgehalt anhand der Aufschrift auf Nahrungsmittelpackungen (Foodlabels, FL) evaluiert.
Methodik: 459 Besucher (m/f = 275/148, Alter 47 ± 17,3 Jahre, BMI 24 ± 3,8 kg/m^2, Mittelwerte ± SD) des Präventionsbuses der Lungenliga Zürich wurden mittels eines strukturierten Interviews nach dem Verständnis und der Anwendung von FL befragt. Ein Orginal-FL wurde zur Interpretation vorgelegt u.a. zur Angabe resp. Berechnung des Salzgehaltes basierend auf den Angaben des FL (i.e. dem aufgelisteten Natriumgehalt).
Resultate: Der korrekte NaCl Gehalt gemäss Foodlabel konnte von 5 Personen (1,2%) richtig angegeben werden, 418 (98,8%) kamen zu

einem falschen Ergebnis. 154 der befragten Studienteilnehmer (36,4%) wussten den Zusammenhang zwischen Natrium und Salz nicht. 4 Personen, welche das richtige Ergebnis erhielten, verfügten über einen Hochschulabschluss, 1 Person absolvierte eine Berufslehre.
Diskussion: Die vorliegende Arbeit zeigt, dass das Verständnis der Angaben der Nahrungszusammensetzung bezüglich des Natrium- respektive Salzgehaltes unverständlich sind. Ein weiterer Grund für die «Unverständlichkeit» ist aber auch das fehlende Ernährungs-Grundwissen um Empfehlungen umzusetzen. Um das Risiko chronischer Erkrankungen präventiv angehen zu können, sollten nicht nur Ernährungsempfehlungen gemacht werden, sondern es sollte anwendbares Ernährungswissen vermittelt werden.

P34

Quelle information sur le paracétamol d'un simple clic sur Internet?

Piguet V., Cedraschi C., Besson M., Chabert J., Luthy C., Dayer P., Desmeules J. (Genève)

Contexte: Internet offre un volume énorme d'informations sur les médicaments largement utilisées par le public. La qualité des sites concernant les médicaments n'est pas bien définie alors qu'Internet joue un rôle croissant dans l'information et la prise de décision des patients au sujet de leur traitement. Cette étude évalue, selon des critères de qualités reconnus, les informations concernant le paracétamol fournies sur des sites facilement accessibles sur Internet.
Méthode: évaluation de la qualité de 140 sites obtenus par le moteur de recherche Google à partir du terme «paracétamol» ainsi que de 17 noms de marque de médicaments contenant du paracétamol et vendus en Suisse. Des scores ont été établis sur la base des échelles DISCERN et Netscoring, développées dans le contexte de l'évaluation des informations destinées aux patients à propos de la santé et des traitements. Ces scores jugent d'une part le contenu en termes d'objectifs et de crédibilité et d'autre part des aspects liés au design et à l'interactivité du site, au moyen d'échelles de Likert. Deux codeurs indépendants ont procédé à l'évaluation, l'accord s'est avéré très bon (K >0,85).
Résultats: Les sites sont d'origine diverses: 80% commerciale et/ou à but lucratif; 7% association non lucrative; 6% gouvernementale; 5% blog et forum personnels; 2% universitaire. Des annonces publicitaires apparaissent sur 50% des sites. Les scores mesurant la qualité du contenu et de la forme des sites sont faibles: moyennes 20 (DS 17) pour le score DISCERN (score = 16 à 80) et de 108 (DS 40) pour le score Netscoring (score = 0 à 312). Des inexactitudes voire des erreurs pharmacologiques ont été relevées dans 5% des sites (e.g. mode d'action, posologie et interactions).
Conclusion: selon les critères définis, la majorité des sites offrent une information de qualité moyenne voire anecdotique et bombardent les visiteurs de publicités diverses sans relation avec l'information recherchée. Aucun site ne présente une information de qualité intégrant tous les potentiels originaux offerts par cette nouvelle technologie de communication.

P35

Impact sur le personnel d'une interdiction totale de fumer dans un hôpital

Humair J.P., Benz Duborgel V., Mascarini J., Kupferschmid S., Scherrer F., Borrero P. (Genève)

Introduction: L'interdiction de fumer dans les lieux publics et de travail est une stratégie efficace pour réduire l'exposition à la fumée passive et la prévalence du tabagisme. Cette étude évalue l'impact de cette politique aux Hôpitaux Universitaires de Genève (HUG) sur le personnel et le comportement des employés fumeurs.
Méthodes: Depuis le 1.1.2006, les HUG ont adopté une interdiction totale de fumer à l'intérieur des locaux. Elle comprend aussi une campagne d'information, une interdiction de la vente de tabac, la mise en place d'une signalétique aux entrées et de cendriers à l'extérieur, un programme de formation du personnel soignant, d'accueil et de sécurité et des mesures d'aide aux patients et employés fumeurs. On propose aux collaborateurs fumeurs une consultation gratuite d'orientation au service de santé du personnel, l'accès à la consultation de désaccoutumance au tabac et la vente à prix réduit de substituts nicotiniques par la pharmacie. 14 mois après le début de l'interdiction, un questionnaire anonyme, suivi d'un rappel aux non-répondeurs, a été envoyé par courrier à 4500 des 9619 collaborateurs avec un taux de réponse de 64%.
Résultats: La majorité du personnel approuve l'interdiction (92%) et a bien compris qu'on ne peut pas fumer à l'intérieur des locaux (92%). 61,5% des employés sont informés sur les services d'aide à l'arrêt du tabac. La prévalence du tabagisme du personnel a baissé à 15%; comparativement à une enquête de 1999, elle a diminué de 22% à 15% sur le site hospitalier pour soins aigus. 16% des employés fumeurs le 1.1.2006 ont cessé le tabac après cette date, mais peu ont utilisé des services d'aide (4,6%). 49% des fumeurs actuels disent avoir baissé leur consommation de tabac et 71% ont modifié leurs habitudes en prenant leur pause à l'extérieur. Malgré l'interdiction, 27% des collaborateurs sont encore exposés à la fumée passive et 22% en sont gênés.
Conclusions: Après 14 mois, l'interdiction de fumer aux HUG a un impact positif sur le personnel avec une large adhésion à la nouvelle politique et une diminution significative de la prévalence du tabagisme. Mais un non-respect de l'interdiction de fumer persiste à certains endroits avec une exposition importante à la fumée passive. La mise en place d'un hôpital non fumeur est un réel défi nécessitant la poursuite des efforts dans la durée et la recherche de nouvelles stratégies pour faire respecter l'interdiction de fumer et réduire l'exposition à la fumée passive.

P36

Implementing a program of supportive care in cancer through collaborative action

Luthy C., Chouiter A., Konrad-Mugnier B., Grivel A., Delaloye S., Cedraschi C., Allaz A.F. (Geneva)

Aim: Confronted with cancer patients undergoing multiple treatments, we describe the development, implementation, and progress of an in-hospital supportive care program to improve the quality of care.
Setting & Method: The program was implemented in the Division of General Medical Rehabilitation of the Geneva University Hospitals, in collaboration with the Division of Oncology. The following priorities were identified: 1) reduce the morbidity related to the disease and the treatment; 2) improve the quality of life; 3) improve hospital coordination of care and psychosocial support; 4) provide continued education and supervision for the team; 5) develop follow-up indicators (i.e. expectations and needs of the patients, satisfaction with care, adjustment to the disease and coping strategies).
Description of the program: Various actions were taken: initiating regular multidisciplinary staff meetings; developing new strategies to organize day-to-day patients' care (pain management, nutrition, psychological support); implementing guidelines and improved data collection forms for the health care providers; elaborating leaflets for patients. A database has been implemented to allow for the characterization of the patients. Diverse educational interventions were conducted. Special off-site seminars and tutorials were offered to the medical and nursing team in collaboration with ambulatory and in-hospital expert partners (e.g. specialised training for specific devices, administration of chemotherapy, massage therapy, psychological supervision). A particular emphasis was put on sharing information and discussing the program in order to promote collaborative work within the team and to address the specificities of the aims and contents of the supportive care program in the clinical pathway.
Discussion: The implementation of such a supportive care program highlights some of the challenges faced by health professionals when attempting to improve the quality of care in this field as well as the extent of their needs. Clinical mentors have proven to be a key factor in effecting day-to-day practice and to empower nurses. Such a program requires considerable time and energy to plan actions and tasks according to the available knowledge and know-how, to acknowledge and positively reinforce these competences and to develop them where and when necessary and possible.

P37

Changer le fonctionnement médical d'un service de médecine interne et réaliser des économies: le défi relevé

Hagmann N., Burnand J., Calderari F., Schnorf M., Waeber G., Lamy O. (Lausanne)

Introduction: Les coûts de la médecine hospitalière continuent à augmenter. Différents types d'interventions ont montré la possibilité de les diminuer: guidelines pour diminuer les durées moyennes de séjours (DMS), contrôler la prescription médicamenteuse, etc. Le but de notre étude est de tester un fonctionnement différent et autonome d'une unité de médecine et d'en mesurer les effets en améliorant les interfaces (équipe infirmière, secrétariat).
Méthode: Nous avons comparé prospectivement le fonctionnement d'une unité standard (US) témoin de médecine interne générale universitaire aiguë à celui d'une unité autonome (UNAU) en modifiant l'organisation médicale. L'US a 27 lits, l'UNAU 25, et les deux unités accueillent le même type de patients. Pendant les jours ouvrables, l'US fonctionne avec trois médecins assistants (MA) et un chef de clinique (CDC), et l'UNAU avec un MA aîné, un CDC et une assistante médicale, en respectant le cadre horaire défini. Plusieurs indicateurs ont été suivis: DMS, mortalité, coûts des examens paracliniques, etc.
Résultats: Du 1er avril 2006 au 31 mars 2007, 1335 patients ont été hospitalisés dans les deux unités. Ils étaient identiques en terme d'âge et de sexe dans les deux unités. La DMS était de 12,2 jours dans l'UNAU et de 11,6 dans l'US (ns). La mortalité était respectivement de 4,4% et de 6,1%. L'économie salariale annuelle était de CHF 110 577.– dans l'UNAU. Les coûts par patient des examens paracliniques ont diminué de 21 à 25% dans l'UNAU: radiologie CHF 414.– vs 553.–; chimie clinique, hématologie et immunologie CHF 421 vs 532.–; examens microbiologiques CHF 131.– vs 166.–. Pour un service de médecine interne générale de 25 lits, l'économie annuelle réalisée en tenant compte uniquement des salaires de l'équipe médicale, des examens de radiologie et de laboratoire (chimie, hématologie, etc.) est de CHF 336 593.–. L'organisation du travail est meilleure dans l'UNAU (respect des horaires) que dans l'US. La satisfaction du personnel soignant de l'UNAU était meilleure après l'introduction du nouveau mode de fonctionnement. Les médecins de l'UNAU ont suivi moins d'heures de formation post-graduée que ceux de l'US.
Conclusion: Si ce mode de fonctionnement autonome offre des avantages économiques et en terme de satisfaction, des améliorations sont à apporter sur la formation des médecins. L'absence d'effet sur la DMS s'explique probablement par l'âge élevé des patients et les nombreuses co-morbidités.

P38

Prise en charge de la douleur aiguë aux urgences: impact d'un soutien informatique sur la documentation de la douleur

Hugli O., Palhais N., Achour S., Tamchès E., Trueb L., Yersin B. (Lausanne)

Un hiatus perdure entre les recommandations de pratique clinique (RPC) pour l'antalgie aux urgences et leur mise en pratiques par les soignants (1). Or de nombreux centres d'urgences emploient une application informatique pour la gestion clinique de leurs patients (flux, recueille de données cliniques, notamment l'intensité de la douleur). But de l'étude: déterminer si le développement d'un module informatique spécifiquement dédié à la prise en charge de la douleur améliore la documentation de la douleur aiguë aux urgences.
Méthode: Étude prospective pré- et post-mise en place d'un algorithme activant l'ouverture automatique de fenêtres surgissantes (pop-up) par notre application informatique au tri et en zones de soins; les fenêtres contenaient des messages enjoignant les soignants à évaluer la douleur et à suivre son évolution; l'algorithme gérant ces fenêtres est basé sur les RPC de notre service (2). Critères d'évaluation de l'intervention: documentation et quantification de la douleur au tri, et dans les zones de soins. Données recueillies automatiquement par l'application informatique, complétées par données recueillies dans le dossier médico-infirmier et auprès du patient. Inclusion de tous patient >= 16 ans admis avec une douleur de <8 jours ou ayant développé une douleur aux urgences. Analyses par statistiques descriptives habituelles; comparaison pré et post-intervention par test exact de Fisher pour les proportions, par test de t pour échantillons non-appariés pour les valeurs continues. Une valeur de p bilatéral <0,05 indicateur de différence significative.
Résultats: 203 patients ont été inclus en phase pré et 219 en phase post-intervention; patients similaires pour l'âge (43 et 45 ans; p = 0,65), la proportion de femmes (48 et 47%; p = 0,72), et l'intensité de la douleur à l'admission par échelle visuelle analogique (6,2 et 6,0 cm; p = 0,6). La documentation de la douleur au tri a passé de 59% à 91% (p <0,001), dans le dossier médical de 26% à 37% (p = 0,013), et de 66% à 81% dans le dossier infirmier (p <0,001). La réévaluation infirmière de la douleur a passé de 37 à 49% (p = 0,01).
Conclusion: le soutien informatique améliore la documentation de la douleur aiguë par les soignants aux urgences, particulièrement au tri. L'étude se poursuit afin de déterminer si l'impact positif se maintient dans le temps.
(1) I. Decosterd et al: Ann Emerg Med. 2007;50:462–71.
(2) E. Tamchès et al. Swiss Med Wkly. 2007;137:223–7.

P39

Soins palliatifs: définitions et pratique

Rivier E., Pfister JA., Frueh D., Bovard CL., Rosselet F., Péclard J. (Vevey, St-Saphorin)

La notion des soins palliaitifs (SP) évolue, ainsi que la frontière entre soins curatifs et SP. Il en va de même des domaines de la médecine dans lesquels des SP peuvent être considérés. Notre équipe a ressenti le besoin de faire table rase des données acquises et de reprendre le problème de façon fondamentale, en s'appuiant sur les livres de référence, sur la littérature médicale et sur les référentiels qualité disponibles de nos jours. Sans prétendre être exhaustif, ce travail débouche sur la pratique que notre équipe entend suivre dans ce domaine, en élaborant de façon détaillée des notions telles que les besoins, la dignité ou l'autonomie d'un patient, la notion de travail en partenariat et en interdisciplinarité, et la démarche qualilté nécessaire pour entreprendre de tels soins.

P40

Inhibition of macrophage phagocytotic activity by a receptor-targeted polymer vesicle-based drug delivery formulation of pravastatin

Broz P., Ben-Haim N., Grzelakowski M., Marsch S., Meier W., Hunziker P. (Basel/Biel, Basel)

Objective: Complications of atherosclerosis such as heart attack and stroke are leading causes of death, but even drugs like statins achieve event reductions of only 30%. Dose-limiting adverse effects in remote organs such as lethal rhabdomyolysis prohibit achieving higher drug levels known to have strong beneficial effects on the cells populating the atherosclerotic plaque, in particular macrophages. We hypothesized that receptor-specific statin targeting using polymer vesicles would allow cell-selective high-dose treatment for improved efficacy, while minimizing toxicity in other cells.
Methods: The statin pravastatin, at high doses known to suppress macrophage lipoprotein (LDL) uptake, a key process in atherosclerosis progression, was packaged into synthetic nanosize polymer vesicles. A ligand for the macrophage scavenger receptor A1 was used for targeting, while the vesicle's stealth properties practically eliminated interaction with other cell types like skeletal muscle cells, responsible for toxicity.
Results: Vesicle uptake by target cells but not other cell types and slow intracellular content release was observed. A major improvement in biologic efficacy, measured as dose with 50% reduction of macrophages active in LDL uptake (ED50), was observed for polymer vesicles compared to free drug (ED50: 0.15 µmol/L versus 11 µmol/L). In contrast, drug toxicity on skeletal muscle cells was apparent at 2–3 times ED50 for free pravastatin, while no toxicity was observed for all pravastatin vesicle concentrations.
Conclusion: Such high-dose, targeted therapy of statins through cell-specific polymer vesicles allows novel treatment paradigms not only for atherosclerosis, but appears promising for a wide range of drugs and diseases.

P41

L'arrêt cardio-respiratoire (ACR) au cabinet médical est-il une réalité et y a-t-il nécessité de s'équiper d'un défibrillateur semi-automatique (DSA)?

Potin M., Pittet V., Staeger P., Vallotton L., Burnand B., Yersin B. (Lausanne)

Introduction: Cette étude a pour but de déterminer la fréquence de survenue de l'arrêt cardio-respiratoire (ACR) au cabinet médical qui constitue un élément de décision quant à la justification de la présence d'un défibrillateur semi-automatique (DSA) au cabinet médical.
Matériel et Méthode: Analyse rétrospective des fiches d'intervention pré-hospitalière des ambulances et des SMUR (Service Mobile d'Urgence et de Réanimation) du canton de Vaud (650'000 habitants) entre 2003 et 2006 qui relataient un ACR. Les variables suivantes ont été analysées: chronologie de l'intervention, mesures de réanimation cardio-pulmonaire (RCP) appliquées, diagnostic présumé, suivi à 48 heures.
Résultats: 17 ACR (9 ♂, 8 ♀) ont eu lieu dans les 1655 cabinets médicaux du canton de Vaud en 4 ans sur un total de 1753 ACR extrahospitaliers, soit 1% de ces derniers. Tous ont motivés une intervention simultanée d'une ambulance et d'un SMUR. L'âge moyen était de 70 ans. Le délai entre l'ACR et l'arrivée sur site d'un DSA était en moyenne de plus de 10 minutes (min-max: 4–25 minutes). Dans 13 cas évaluables, une RCP était en cours à l'arrivée des renforts, mais seulement 7 étaient qualifiées d'efficaces. Le rythme initial était une fibrillation ventriculaire (FV) dans 8 cas et ont tous reçu un choc électrique externe (CEE), dont 1 avant l'arrivée des secours administré dans un cabinet équipé d'un DSA. Le diagnostic était disponible pour 9 cas: 6 cardiopathies, 1 embolie pulmonaire massive, 1 choc anaphylactique et 1 tentamen médicamenteux. Le devenir de ces patients a été marqué par 6 décès sur site, 4 décès à l'admission à l'hôpital et 7 vivants à 48 heures. Les données ne permettent pas d'avoir un suivi ni à la sortie de l'hôpital ni ultérieurement.
Conclusions: Bien que la survenue d'un ACR soit très rare au cabinet médical, il mérite une anticipation particulière de la part du médecin. En effet, le délai d'arrivée des services d'urgences nécessite la mise en œuvre immédiate de mesures par le médecin. En outre, comme professionnel de la santé, il se doit d'intégrer la chaîne de survie en procédant à une alarme précoce du 144 et initier des gestes de premier secours («Basic Life Support»). La présence d'un DSA pourrait être envisagée en fonction notamment de l'éloignement de secours professionnels équipés d'un DSA.

P42

Ergometrie versus Kardiogoniometrie in der Diagnostik der koronaren Herzkrankheit

Schüpbach M., Loretan P., Meier B., Sanz E. (Bern, Zäziwil)

Einleitung: Die Kardiogoniometrie (KGM) ist ein nicht-invasives orthogonales vektorkardiographisches Verfahren, das in der Diagnostik der koronaren Herzkrankheit (KHK) eingesetzt werden kann. Bisherige Daten zeigen einen Vorteil der KGM gegenüber dem Ruhe-EKG für die Sensitivität und die Akkuranz bei gleich hoher Spezifität für beide Methoden. Wir vergleichen die KGM mit dem Belastungs-EKG (Ergometrie) in der Diagnostik der KHK.
Methode: Bei 163 Patienten (53 Frauen), die nach Durchführung einer Ergometrie zu einer elektiven Koronarographie zur Abklärung bei Verdacht auf eine KHK zugewiesen wurden, wurde vor der Koronarographie eine KGM, ein Ruhe-EKG und eine Ergometrie durchgeführt. KGM und Ruhe-EKG wurden nach standardisierten Kriterien und verblindet befundet. Sensitivität, Spezifität und diagnostische Treffsicherheit (Akkuranz) der drei Methoden wurden verglichen. Der angewandte KGM-Score wurde vorgängig prospektiv validiert. Ein verbesserter retrospektiver KGM-Score wurde anschliessend erstellt. Die Ergometrie wurde als positiv gewertet, wenn entweder der klinische oder der elektrische Befund als positiv beurteilt wurde. Die Diagnose einer KHK basierte auf der Koronarographie (Vorliegen signifikanter, d.h. ≥70%iger Stenosen).
Ergebnis: Die Ergometrie hat eine höhere diagnostische Sensitivität (78%) als die Untersuchungen ohne Belastung; die Ergometrie war aber sehr unspezifisch in der untersuchten Kohorte (29%). Die Sensitivität der KGM ist besser als die des Ruhe-EKGs, der anderen nichtinvasiven Untersuchung in Ruhe (51% versus 39%). Die KGM und das Ruhe-EKG sind spezifisch (KGM 92%, EKG 80%). Der revidierte KGM-Score hat eine deutlich höhere diagnostische Sensitivität (71%) bei unverändert guter Spezifität. Die Akkuranz des prospektiv validierten KGM-Scores (67%) ist besser als die der Ergometrie (53%) und des Ruhe-EKGs (56%); die Akkuranz der KGM konnte im revidierten Score weiter verbessert werden (78%). Der positiv (PPV) und negativ (NPV) prädiktive Wert der KGM war höher als derjenige von Ruhe- und Belastungs-EKG (Tabelle).
Schlussfolgerung: Bei Patienten mit Verdacht auf eine KHK, die zur weiteren Abklärung zuerst mit Ergometrie abgeklärt werden, hat die KGM eine höhere diagnostische Treffsicherheit (Akkuranz) und prädiktive Aussagekraft als das Ruhe- und Belastungs-EKG. Die KGM kann als ergänzende diagnostische Methode bei Verdacht auf KHK hilfreich sein, zumal es sich um eine risikolose und wenig aufwendige Untersuchung handelt.

Tabelle

	Sensitivität	Spezifität	Accuracy	PPV	NPV
Ruhe-EKG	39%	80%	56%	72%	50%
Ergometrie	78%	29%	53%	60%	50%
KGM validiert	51%	92%	67%	90%	58%
KGM revidiert	71%	88%	78%	87%	69%

P43

Cryoballon – eine wirksame ablative Therapie des paroxysmalen Vorhofflimmerns

Meyer B.J., Hoffmann P., Maurer M., Raab J. (Bern, D-Landau)

Einleitung: Die Cryoablation von paroxysmalem Vorhofflimmern (PAF) mit dem Cryo-Ballon-Kathetersystem Arctic Front (CryoB) hat sich als sicheres Therapieverfahren zur elektrischen Isolierung der Pulmonalvenenostien (PV) etabliert; ohne dass eine kostensteigernde Kombination mit einer elektrophysiologisch geführten «on-top-Therapie» zur Eliminierung von Restpotentialen mittels zusätzlicher Ablationskatheter erforderlich ist. Wir untersuchten in einer Pilotstudie die Therapieeffektivität einer Intervention mit einer CryoBTechnik allein ohne zusätzliche segmentale PV-Ablation auf den Erhalt des Sinusrhythmus (SR) 3 Monate nach Intervention.
Methodik: Es wurden 6 konsekutive Patienten (1 Frau, 5 Männer, Alter 62,7 ± 10,9 J.) eingeschlossen, die an einem therapierefraktären (3,0 ± 1,0 Antiarrhythmika) PAF von 71 ± 62 Monaten Dauer litten. Die transseptale PV CryoB-Ablation erfolgte mit Hilfe der angiographischen Darstellung und Dichtigkeitskontrolle (Kontrastmittel-Washout) der entsprechenden PV. Der Therapieeffekt wurde nur selektiv mit Elektroden-Kathetern geprüft. Patienten, die im 3-Monats-Follow-up PAF-Rezidive aufweisen, wird ein Zweiteingriff mit gleicher Technik (kleinere Ballongrösse) und Touch-up angeboten.

Primärer Endpunkt war Sinusrhythmus im 3 Monats FU (Dokumentation mittels 12-Kanal-EKG, 24h-Langzeit-EKG, Ereignis-Recorder, Arrhythmieanamnese).
Ergebnisse: Es wurden 24 Pulmonalvenen mit insgesamt 48 Cryo-Applikationen behandelt (2,0 ± 0,0 Cryoabgaben pro PV). Hierdurch konnten 100% der Pulmonalvenen isoliert werden (angiographisch-anatomische Kontrolle). Die Interventionsdauer betrug 162 ± 21 min. Komplikation wie Paresen des N. phrenicus, Koronarläsionen oder Thromboembolien traten nicht auf. Nach 112 ± 52 Tagen wiesen 100% (n = 6) der Patienten SR auf. Bei einem Patienten traten häufige Episoden von Vorhofflattern auf; ein Zweiteingriff mittels klassischer Isthmusablation führte zur Arrhythmiefreiheit. Mittlere Arzt- und Spitalkosten: CHF 17'900 (€ 7400).
Schlussfolgerung: Eine alleinige Cryoballon-Therapie mit dem Arctic Front System erreicht bei Patienten mit paroxysmalem Vorhofflimmern eine 3-Monats-Erfolgsrate die mindestens vergleichbar ist mit der Radiofrequenz-Standardtherapie. Gemäss den zweijährigen internationalen Erfahrungen ist die Methode sicher und kann bei Patienten mit entsprechender Indikation nach den neuesten Richtlinien mit vergleichbar geringem Zeitaufwand und mit vertretbaren Kosten zur Anwendung kommen.

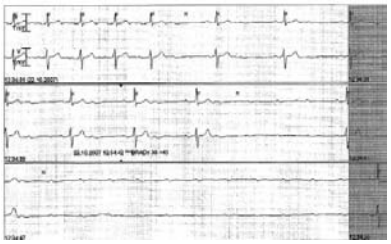
P44

Akute Cholezystitis und kompletter AV-Block. Koinzidenz oder gibt es einen kardiobiliären Reflex?

Franzen D., Jung S., Fatio R., Brunckhorst C. (Zollikerberg, Zürich)

Akute Cholezystitiden sind selten (auch ohne strukturelle Herzerkrankung) mit EKG-Veränderungen, wie Arrhythmien oder unspezifischen ST-T-Alterationen assoziiert. Ein kompletter AV-Block ist in diesem Zusammenhang eine Rarität.
Wir berichten über einen 48-jährigen bis anhin gesunden Patienten, welcher sich wegen massiver Oberbauchschmerzen im Rahmen einer akuten Cholezystitis vorstellte. Bei normalem Eintritts-EKG wurde die Indikation zur Cholezystektomie gestellt. Präoperativ erlitt der Patient zweimalige Synkopen mit nachfolgendem Bewusstseinsverlust von mehreren Sekunden, weshalb eine telemetrische EKG-Überwachung durchgeführt wurde. In der Aufzeichnung (Abb.) zeigte sich dann ein Übergang eines AV-Block 2. Grades (2:1) in einen kompletten AV-Block ohne Ersatzrhythmus mit einer Dauer von 9 Sekunden, was weder beobachtet noch subjektiv wahrgenommen wurde. Serologisch und elektrokardiografisch fanden sich keine Hinweise für ein akutes koronares Syndrom. Nach laparaskopischer Cholezystektomie einer gangränös veränderten Gallenblase wurde der Patient schliesslich während 4 Tagen telemetrisch überwacht ohne weitere synkopale oder rhythmogene Ereignisse. Die transthorakale Echokardiografie, das Belastungs-EKG, die Carotis-Massage und die Koronarangiografie waren unauffällig. Die elektrophysiologische Untersuchung zeigte eine unauffällige AV-Knotenphysiologie mit normaler HV-Zeit. Auf eine Schrittmacherimplantation wurde daher verzichtet. Der Patient ist auch 3 Monate nach dem Ereignis wohlauf und frei von Synkopen oder Schwindel. Synkopale Ereignisse im Rahmen eines vasovagalen Reflexes sind bei massiver Schmerzsensation bekannt. Auch im Rahmen einer akuten Cholezystitis wurden bereits von Synkopen mit Bradykardie und Hypotonie oder von asymptomatischen EKG-Veränderungen berichtet. Ursächlich wird dafür ein vagal vermittelter kardio-biliärer Reflex im Rahmen der Gallenblasendehnung postuliert. Durch die Vagusreizung entstehende AV-Blockierungen sind schon mehrfach beschrieben worden. Ein kompletter AV-Block im Rahmen einer akuten Cholezystitis wurde erst einmal beschrieben, wobei es nach der Cholezystektomie ebenfalls zum spontanen vollständigen Verschwinden der AV-Blockierung kam. Ein abwartendes Verhalten ohne Schrittmacherimplantation kann daher nach Ausschluss aller anderen Ursachen in dieser Situation empfohlen werden.

Abb. 1
Telemetrie-EKG



P45

Buccal skinfold thickness – a proxmarker for body fatness and fat distribution

Thaler Th., Suter P.M. (Zürich)

Background: Obesity is characterized by an increase in fat mass. Usually in the setting of overweight and obesity fat is deposited in all body locations. Abdominal obesity – reflected in an increased waist circumference – is associated with an increased health risk. A positive relation exists between the body mass index (BMI), the total fat mass (TFM) as well as the waist circumference (WC). For cultural reasons patients often do not want to undress or refuse even anthropometric measurements. In this study the relationship between buccal skin fold thickness (BSF) with TFM, BMI and WC was studied in young adults.
Methods: 409 students (m/f = 179/230) at the age of 15–22 years (BMI 21.09 ± 1.81 kg/m^2) were examined. Body weight, WC and BMI were measured according to the usual guidelines. The BSF was measured vertically in the middle of cheek between tragus and angulus oris using a calliper (Holtain LDT Crymych, UK). The average of three measurements was used. TFM was determined by bioimpedance (Tanita BF-410, Japan).
Results: The correlation coefficient (r) for the relationship between the different variables was for males/females: BSF (mm) and kg: 0.44/0.35
BSF (mm) and BMI (kg/m^2): 0.43/0.36
BSF (mm) and WC (cm): 0.48/0.4
BSF (mm) and TFM (%): 0.47/0.35
p for all <0.01
Discussion/conclusions: A significant relationship was found between BSF and body weight, BMI, WC and TFM. The relationship was strongest between BSF and WC in male (r = 0.48). Our data suggest that the measurement of the BSF might be a useful easy accessible proxy marker for the assessment of fat distribution in patients who do not want anthropometric measurements for cultural reasons.

P46

Prevalence of sub-clinical atherosclerosis across age and gender in West of Switzerland

Depairon M., Stauffer I., Berthoud M., Darioli R. (Lausanne)

Atherosclerosis (ATS) is a focal and disseminated disease of arterial wall with asymptomatic progression for many years until its first clinical manifestation such as an acute coronary syndrome or a stroke. Since more than 60% of victims of a first cardiovascular events (CVE) were stratified with a coronary risk of less than 20% of risk, clinicians should consider other tests to identify high risk patients (HR-P). Among them, B-mode ultrasounds on carotid was developed to predict the risk of CVE beyond the traditional RF assessment alone. However, epidemiological data on subclinical atherosclerosis are lacking. The purpose of this prospective study was to evaluate the prevalence of subclinical atherosclerosis on femoral and or carotid atherosclerosis across age and gender among adults.
The study population included 1620 asymptomatic patients aged from 20 to 70 years (mean = 48 ± 12), without established CVD, who were consecutively referred from West of Switzerland for therapeutic advices. Cardiovascular risk factors (CV-RF) were systematically screened for each subject, including medical history, physical examination and clinical chemistry. B-mode ultrasounds on carotid and femoral arteries was performed by two investigators to detect atherosclerotic plaques (focal thickening of intima-media >1.2 mm). The prevalence of ATS achieved respectively 61% in men and 48% in women (p <0.001), with a significant correlation with the number of the traditional CV-RF (r = 0.31, p <0.001). However, no ATS was detected in 30% of P with >3 CV-RF. As illustrated in the table 1, there was an increased prevalence of ATS across age in both genders (p <0.001).

Table 1
Prevalence of subclinical atherosclerosis across age and gender

Age (yr)	20–29	30–39	40–49	50–59	60–70
Women (n = 641)	5.5%	18.1%	42.4%	61.0%	77.6%
Men (n = 979)	6.1%	35.2%	60.1%	73.3%	88.9%

In conclusion, the results indicate that, beyond the epidemiology of the traditional CV-RF, more research should be performed on subclinical ATS in order to improve the primary prevention of CVD.

P47

Impact of renal function on long-term mortality of ICD patients with nonischemic heart disease

Wolber T., Schefer T., Binggeli C., Holzmeister J., On C.-J., Brunckhorst C., Duru F. (Zürich)

Background: Randomized trials have demonstrated that implantable cardioverter defibrillator (ICD) therapy may reduce the risk of death in patients with nonischemic cardiomyopathy. However, the long-term benefit of ICD therapy in a routine clinical setting has not been investigated in these patients.
Methods: We performed a single-center longitudinal study to assess the outcomes of 176 patients with nonischemic cardiomyopathy who were implanted with an ICD for primary or secondary prevention of cardiac death.
Results: The cumulative survival rate after 1, 2, 5 and 10 years was 91%, 87%, 78%, and 65%. Mortality risk was similar among patients with primary and those with secondary prevention indication for ICD implantation. Atrial fibrillation, recurrent ventricular arrhythmias requiring ICD therapy, and right ventricular pacing, but not delayed intrinsic ventricular conduction was associated with higher risk. Impaired systolic left ventricular function with ejection fraction <35% (HR 3.3, p = 0.01), New York Heart Association (NYHA) functional class >= III (HR 2.5, p = 0.03), and renal insufficiency with estimated glomerular filtration rate < 60 ml/min/1.73 m^2 (HR 5.9, p <0.001) were independent predictors of mortality.
Conclusion: In ICD patients with non-ischemic cardiac disease, atrial fibrillation, recurrent ventricular arrhythmias, and right ventricular pacing are associated with adverse outcome. Impaired left ventricular function, NYHA functional class and renal insufficiency are independent predictors of mortality. Patients with impaired renal function are at highest risk.

P48

Paradoxe Koronarembolie und Lungenembolien bei einem Patienten mit hereditärer hämorrhagischer Teleangiektasie

Frasnelli M.E., Müller-Burri S.A., Kurz D.J., Tüller D., Eberli F.R., Brühlmann W., Meier C.A. (Zürich)

Fall: Ein 46jähriger Patient mit hereditärer hämorrhagischer Teleangiektasie (HHT) wurde knapp eine Woche nach einer Meniskektomie wegen Thoraxschmerzen und Dyspnoe beim Hausarzt vorstellig. Bei inferiorem ST-Hebungs-Myokardinfarkt im EKG zeigte sich in der Koronarangiographie ein distaler Verschluss des R. interventricularis posterior bei sonst nicht relevanter Koronaratheromatose. Die wegen persistierender Beschwerden durchgeführte Computertomographie ergab parazentrale Lungenembolien und mehrere, für die HHT typische, pulmonale arteriovenöse Malformationen (AVM). Nach Ausschluss eines intrakardialen Shunts und eines offenen Foramen ovale interpretierten wir den Verschluss des R. interventricularis posterior als Folge einer paradoxen Embolisation über die AVM im Rahmen eines durch die postoperative Immobilisation getriggerten thromboembolischen Ereignisses. Nach interventionellem Verschluss der pulmonalen AVM mittels Coils wurde der Patient mit einer oralen Antikoagulation entlassen.
Diskussion: Die HHT (Osler-Weber-Rendu Syndrom) ist mit einer Inzidenz von 1/5000–8000 eine seltene, autosomal dominant vererbte Krankheit. Mutationen im Gen für Endoglin oder activin-receptor-like kinase 1 (ALK1) führen zu Gefässmissbildungen in verschiedenen Organen. Charakteristisch für die HHT sind mukokutane Teleangiektasien, Epistaxis, gastrointestinale Blutungen und eine Eisenmangelanämie. Etwa 30% der Patienten zeigen zudem AVM der Lunge und/oder der Leber und etwa 10–20% im ZNS. Häufige Komplikationen der pulmonalen AVM sind hämodynamisch relevante rechts-links Shunts, Blutungen (Hämoptyse, Hämatothorax) und paradoxe Embolien mit Hirnabszess und -infarkt. Bei den vereinzelt beschriebenen kardialen Komplikationen der HHT handelte es sich jeweils um ischämische Ereignisse bei Aneurysmata der Aa. coronariae. Unser Fall beschreibt erstmals das Auftreten eines Myokardinfarktes bei einem Patienten mit HHT als Folge einer paradoxen Embolie. Dabei waren die pulmonalen AVM die pathogenetische Verknüpfung, welche zum gleichzeitigen Auftreten der Lungenembolien und des Herzinfarktes führte.

P49

Mikroalbuminurie bei Hypertonikern in der Schweizer Hausarztpraxis und Reduktion durch Telmisartan Eine offene Beobachtungs- und Risikostratifizierungsstudie bei 827 Hypertonikern

Martina B., Barth P., Tetyusheva M., Diedrich J.P. (Basel, Freiburg i.Br.)

Einleitung: Jeder 2. Hausarztpatient hat eine arterielle Hypertonie. Bereits 50% dieser Hypertoniker befinden sich in einer Hochrisikosituation. Dazu haben 25% aller Hypertoniker eine Mikroalbuminurie (**MA**), die isoliert schon eine Hochrisikosituation darstellt. Dennoch wird die MA generell viel zu selten bestimmt, obwohl gerade Patienten mit bestehender MA zur Prognoseverbesserung eine gezielte medikamentöse Therapie benötigen. Der Angiotensin-II-Antagonist Telmisartan reduziert die MA bei Diabetes, Nephropathie und Hypertonie. Wir berichten über eine grössere hausärztliche Beobachtungsstudie mit Hypertoniepatienten, bei welchen der Verlauf der MA unter Therapie mit Telmisartan untersucht wurde.
Methoden: Bei 827 Hausarztpatienten (in 129 Schweizer Praxen) mit diagnostizierter Hypertonie wurden das kardiovaskuläre Risiko und die MA (Quotient: Albumin/Kreatinin im Urin) vor Beginn und 4 Monate nach Therapieumstellung auf Telmisartan untersucht. 57% der Patienten wurden mit Telmisartan und 41% mit Telmisartan/HCTZ behandelt. Eine Risikostratifizierung wurde nach den WHO/ISH 99/2003 Kriterien vorgenommen (ein sehr hohes Risiko bedeutet ein >30%iges, ein tiefes Risiko ein <15%iges Risiko für das Auftreten eines Hirnschlags oder Herzinfarktes innerhalb der nächsten 10 Jahre). Veränderungen von Blutdruck und MA wurden mit Hilfe des parametrischen T-Tests geprüft.
Resultate: Die Hypertoniker waren im Mittel 60 (18–95) Jahre alt; 52% männlich. 31% Diabetiker, und 78% hatten ein Hochrisiko aufgrund ihrer Komorbiditäten. 50% wiesen zu Beginn eine MA auf. 56% der Patienten ohne MA erfüllten ebenfalls die Hochrisiko-Kriterien. Der Anfangs-Blutdruck betrug 160+15 / 96+10 mm Hg und fiel nach 4 Monaten Behandlung mit Telmisartan signifikant auf 138 + 10 / 84 + 7 mm Hg (p <0,0001). Die MA reduzierte sich nach 4 Monaten Therapie mit Telmisartan bei den Patienten ohne vorbehandelte Hypertonie signifikant von 9,5 + 16 mg/mmol auf 6,5 + 13 mg/mmol und bei den vorbehandelten Patienten von 8,7 + 14 mg/mmol signifikant auf 6,1 + 11 mg/mmol (beide p <0,0001).
Konklusion: Sehr viele Hypertoniker in Hausarztpraxen sind Hochrisikopatienten. Diese Feststellung entspricht Ergebnissen der hausärztlichen schweizerischen Hypertoniekohorte und Untersuchungen anderer europäischer Länder. Wenn, wie in vorliegender Untersuchung, zusätzlich die MA bestimmt wird, steigt der Anteil der behandlungsbedürftigen Hochrisikopatienten auf 78% an. Die Ergebnisse unterstreichen die unterschätzte Bedeutung der gezielten MA-Bestimmung in der Hausarztpraxis. In unserer Untersuchung wurde ferner gezeigt, dass bei hausärztlichen Hypertonikern durch Therapie mit Telmisartan neben einer starken Blutdrucksenkung das Mikroalbumin im Urin, hochsignifikant gesenkt werden kann.

P50

An unusual case of congestive heart failure

Manser C.N., Zbinden R., Meier C.A., Gerber B. (Zürich)

We report the case of a 52 year old female diabetic patient with known sensorineural hearing-loss, presenting with congestive heart failure and severe lactic acidosis. Echocardiographic findings revealed severe systolic and diastolic dysfunction and a strikingly hyperechogenic myocardium, suggesting restrictive, infiltrative cardiomyopathy. Common systemic illnesses showing cardiac envolvement, such as amyloidosis, storage diseases and iron overload, could be ruled out. The combination of restrictive cardiomyopathy, diabetes mellitus, deafness and sustained lactic acidosis finally led to the hypothesis of a mitochondrial disorder which was confirmed by genetic testing. Analysis of mitochondrial (mt) DNA showed an A-to-G mutation in the tRNALeu(UUR) gene at nucleotide position (np) 3243. This mt DNA 3243(A-G) mutation has originally been reported in patients presenting with mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS), but is also known to be associated with early onset diabetes mellitus. Some authors even claim that this mutation may be present in up to 0.5–2,8% of the diabetic population. Clinical findings in patients with mt DNA 3243 (A-G) mutation are heterogenous: A Japanese study of 113 mutant diabetic patients demonstrated neurosensory deafness in 92%,

basal-ganglia calcification in 71%, neuromuscular disorders in 23% and neuropsychiatric disturbances in 16% of all cases. Cardiomyopathy was present in 30% of all patients with dilated (18%) and hypertrophic (8%) cardiomyopathy being the most common disorders. Cardiac conduction abnormalities were detected in 27%. Even though cardiomyopathy seems to be an important complication in patients with mt DNA 3243(A-G) mutation, it appears to be even more common in mt DNA 3260(A-G) and 3303(C-G) mutations.
Conclusion: In restrictive cardiomyopathy a mitochondrial disorder should be considered if a combination of clinical features such as early-onset diabetes, hearing loss, lactic acidosis and neuropsychological abnormalities is present. Genetic counselling of affected individuals and families is essential.

P51

Fünf Fälle einer Thrombolyse unter CPR nach fulminanter Lungenembolie mit Kreislaufstillstand

Frank B., Mang G. (Männedorf)

Wir präsentieren eine Serie von fünf Patienten, welche in den letzten 4 Jahren in unserer Klinik einen Kreislaufstillstand (PEA) aufgrund einer fulminanten Lungenembolie (LE) erlitten hatten und unter cardiopulmonaler Reanimation (CPR) einer Thrombolyse unterzogen wurden.
Methode: Zusammenstellung aller Fälle, welche im Spital Männedorf seit 2003 nach einem Kreislaufstillstand aufgrund einer LE unter CPR thrombolysiert worden sind. Mit Blick auf die Anamnese, das Outcome und Komplikationen. Das Vorgehen wurde gewählt, wenn aus der unmittelbaren Anamnese eine LE vermutet werden musste, oder eine solche durch indirekte echokardiographische Zeichen hochwahrscheinlich war und die konventionellen Massnahmen der CPR nicht zum Wiedererlangen eines spontanen Kreislaufes geführt hatten. Die Lyse wurde mit Alteplase durchgeführt. Im Anschluss daran erfolgte die therapeutische Liqueminisierung.
Resultate: Bei sämtlichen Patienten konnte initial ein suffizienter Kreislauf wiedererlangt werden. In keinem Fall wurden Blutungskomplikationen beobachtet, obschon eine Patientin 3 Tage zuvor einem grossen viszeralchirurgischen Eingriff unterzogen worden war (Whipple Operation). 4 der 5 behandelten Patienten überlebten und konnten aus dem Spital entlassen werden, 1 Patientin verstarb wenige Stunden post reanimationem am Rechtsherzversagen. 3 Patienten zeigten keine neurologischen Defizite, 1 Patientin litt während 2 Wochen an einem regredienten, brachial betonten motorischen Hemisyndrom der linken Seite, welches jedoch nach einem Monat nicht mehr objektivierbar war.
Schlussfolgerung: Ein Kreislaufstillstand nach fulminanter Lungenembolie hat eine schlechte Prognose, die Literatur spricht von Überlebensraten unter 40%. Unsere Serie zeigt, dass die Thrombolyse nach erfolgloser konventioneller CPR die Prognose verbessern kann, dies betrifft sowohl das Überleben als auch das neurologische Outcome. Ausserdem konnte gezeigt werden, dass dieses Vorgehen auch Patienten im unmittelbar postoperativen Status nicht a priori vorenthalten werden sollte, da es nicht obligat zu Blutungskomplikationen kommt. Unsere Ergebnisse decken sich weitgehend mit der vorhandenen Literatur, sowie mit den Reanimationsrichtlinien von 2005 des European Resuscitation Council.

P52

Premature coronary heart disease due to a codon 84 nonsense mutation of the apolipoprotein A-I gene

Zimmermann S., Hayoz D. (Fribourg)

Apolipoprotein A-I (apo A-I) deficiency leading to low or very low HDL cholesterol levels is a cause of increased risk of coronary heart disease, restenosis after angioplasty and death from cardiovascular causes. Affected patients have a primary depression in HDL cholesterol to below the tenth percentile compared with age and sex-matched controls. A disturbance in lipoprotein metabolism is often familial. We report the case of a 28 year old male patient, without any know cardiovascular risk factors, who presented with acute coronary syndrome (NSTEMI with troponin Ic elevated to above the normal range to >6 mcg/l). Cardiac ultrasonography revealed moderate inferobasal left ventricular hypokinesia, with normal ejection fraction, and cardiac CT scan demonstrated moderate coronary atherosclerosis. LDL cholesterol levels were found to be extremely low at 0.23 mmol/l (HDL3 subfraction), with total cholesterol (3.4 mmol/l), LDL cholesterol (2.29 mmol/l) and triglyceride levels (1.72 mmol/l) in the normal range. Testing on first-degree relatives of the proband showed that both mother and father had low HDL cholesterol levels (0.55 mmol/l and 0.66 mmol/l, respectively). One paternal uncle and two maternal uncles had low HDL cholesterol levels (0.59 mmol/l, 0.69 mmol/l, and 0.71 mmol/l, respectively). Genetic analysis on the proband (sequencing after amplification) revealed a new nonsense mutation on codon 84 (Q84R, glutamine to arginine) of the apolipoprotein A-I gene, a site previously identified for a Q84X mutation leading to premature CV events. Not only has this mutation never been previously reported, but the proband is homozygous. Homozygosity for codon 84 nonsense mutation should be considered the cause of the low HDL cholesterol levels in the present case. We are currently analysing the kindreds, several among which present with premature coronary heart disease, to understand the segregation of this new hypoalphalipoproteinemia. Furthermore, this new mutation could be added to the list of relevant mutations that are searched for in cases of familial apolipoprotein A-I deficiency.

P53

Left ventricular diverticulum associated with Tako-Tsubo cardiomyopathy: role of cardiac MRI

Oberson M., Wyttenbach R., Di Valentino M., Santini P., Moccetti M., Gallino A. (Bellinzona)

Clinical case: We report the case of a 61-year-old woman with atypical chest pain associated with typical ECG changes (T-wave inversion in V2-V6 and I-II-aVL; with left ventricular apical dysfunction at transthoracic echocardiography and normal cardiac enzymes. Coronary angiography was normal. At left ventricular angiography the apical akinesia was confirmed and was associated with the presence of a large antero-basal diverticulum of the left ventricle. At cardiac magnetic resonance (CMR) performed 7 days after admission, the dyskinetic dysfunction disappeared completely and there was no evidence of delayed enhancement suggestive for fibrosis due to previous myocardial infarction or inflammation. CMR also confirmed the presence of an antero-basal, left ventricular trabeculated diverticulum communicating with the left ventricle by a large “collet” and exhibiting a synchronous contraction with the left ventricle. No paradoxical systolic expansion was appreciated. The patient was treated with atenolol, enalapril and aspirin. At a follow-up visit after 2 months, the patient complained of no symptoms, ECG was normal.
Conclusion: Our case is compatible with a form of Tako-Tsubo cardiomyopathy associated with the unusual concomitant presence of a large antero-basal diverticulum. CMR was crucial in defining localization and morphology of the left ventricular diverticulum. CMR was also important in detecting and clearly defining the transitory dyskinetic apical area without evidence of late enhancement.

P54

Extrinsic compression of the pulmonary artery by a large mediastinal mass: the role of TTE in the decision making for urgent thoracic surgery

Oberson M., Menafoglio A., Guerra A., Alerci M., Zucca E., Di Valentino M., Moccetti M., Mazzucchelli L., Gallino A. (Bellinzona, Locarno)

Clinical case: We report the case of a 19-year-old man, ice-hockey player who presented with a 2-months history of asthenia and non-specific chest pain. At admission, EKG was completely normal, clinical evaluation did not reveal evident signs of infection, bacterial blood cultures remained negative. Laboratory analysis indicated only an elevated ESR, whereas CRP was only slight increased. Chest X-ray

revealed a large mass located in the anterior mediastinum. Urgent transthoracic echocardiography (TTE) showed pulmonary hypertension (45 mm Hg) without enlargement of the right ventricle and confirmed the presence of a large anterior mediastinal hypoechogenic mass compressing the right ventricular outflow tract during diastole. There was a systolic gradient over the right compressed pulmonary artery of 30 mm Hg. These findings were confirmed on subsequent contrast-enhanced multi-detector Computed Tomography (MDCT) of the chest which showed a large tumor of 13 x 8.5 x 8.0 cm which surrounded the outflow tract of the great arteries with severe compression of the right ventricular outflow tract. Due to increased risk of sudden death, an urgent surgical removal of the mediastinal mass followed by a biopsy was successfully performed; the patient recovered immediately and leaved the hospital 4 days later only. Histologically, the tumor was diagnosed as a mediastinal B giant cell lymphoma. The patient was serially followed up with chemotherapy.
Conclusion: This case illustrates the important role of TTE in the decision making of urgent removal of the mediastinal mass.

P55

Systemic arterial embolism in a young body-builder

Moccetti M., Wyttenbach R., Alerci M., Oberson M., Santini P., Di Valentino M., Tutta P., Lepori M., Gallino A. (Bellinzona)

A 31 one year old man without cardiovascular risk factors was referred in 2001 to our emergency division because acute arterial ischemia of the left lower extremity. The patient was a well known bodybuilder (former swiss champion) with active consume of anabolic drugs (positive test in urine for anabolic steroids, negative for cocaine). Screening for thrombophilia was negative and search for embolic sources was negative (TEE) although TTE showed the presence of a small isolated apical hypokinesia without thrombi which was not considered a plausible cause of the clinical picture. The acute ischemia was attributed to a popliteal artery entrapment syndrome with massive hypertrophy of the gastrocnemi muscles and to a putative hypercoagulable state associated with active consume of anabolic drugs. The patient was successfully treated with percutaneous thrombus extraction an local lysis of the popliteal artery. The unusual case was interesting enough to be published as a letter in a peer reviewed journal (N Engl J Med: 2002:346:1254). The patient was discharged with oral anticoagulation for 3 months and the advice to quit the use of anabolic drugs and restrain from body building. The patient was then lost of follow-up. He was admitted urgently in 2007 with bilateral acute ischemia of the lower legs and acute arterial embolism of the left renal artery. The patient underwent successful percutaneous recanalisation of the femoropopliteal arteries and was anticoagulated with e.v non fractionated heparin,clopidogrel and aspirin. He was still an active bodybuilder and anabolic steroid metabolites in urine were again positive.Cardiac MRI showed the presence of a small apical LV akinesia (without visible thrombi) with transmural late enhancement compatible with a previous myocardial infarction. Coronary angiography showed normal epicardial vessels. The hypothesis that the apical akinesia may be the cause of the repetitive arterial embolisations, in absence of other sources, remains the most probable although the cause of the LV apical infarction remains elusive. A contributing factor may be a putative thrombophilic state associated with the use of anabolic steroids. This case show an unusual form of systemic arterial embolisation in a body builder. It also show how during the diagnostic initial reasoning an important finding (LV apical hypokinesia at TTE) may be disregarded while focussing to much on the initial clinical presentation and may mislead from the right diagnosis.

P56

Coronary fibromuscular dysplasia: an elusive diagnosis

Oberson M., Kosmidis S., Mahler F., Alerci M., Wyttenbach R., Tutta P., Di Valentino M., Moccetti M., Sartori F., Gallino A. (Bellinzona)

Fibromuscular dysplasia (FMD) is a disorder that generally affects the renal arteries. Involvement of FMD occurs less often in other arterial territories such as carotid, subclavian, iliac or mesenteric arteries. Involvement of the coronary arteries is extremely rare. A 46-year-old woman with a history of typical chest pain at rest four weeks before admission, was referred by her general practitioner because of the presence of inverted T-waves (in V3-V5). Cardiac enzymes, D-dimer and CRP values, were in the normal range. No atherosclerotic risk factors were present. Coronary angiography showed an isolated (1-1-1 smooth) 60% lesion at the bifurcation of the third diagonal branch of the LAD. Selective angiography of the renal arteries performed during the same invasive procedure, showed the typical pattern of FMD with “string of beads” appearance of the right renal artery. Cardiac-MRI indicated a small area of delayed enhancement compatible with a previous small antero-septal non-transmural myocardial infarction with no evidence of residual myocardial ischemia during adenosine perfusion. Given the association of a single distal lesion of the LAD and the typical pattern of renal FMD, as well as the lack of risk factors, we postulated the tentative diagnosis of coronary FMD, although concomitant “trivial” coronary atherosclerosis cannot be completely excluded.

P57

Après une fracture ostéoporotique: quelle prise en charge et quelle risque de récidive? Résultat d’une enquête lausannoise

Lamy O., Simard N., Krieg M.-A. (Lausanne)

Introduction: L’événement fracturaire est associé à un haut risque de récidive fracturaire. Il se situe, après une année, entre 8 et 20%, selon la localisation de la fracture, l’âge et le sexe des patients. L’introduction d’un traitement spécifique de l’ostéoporose réduit le risque fracturaire vertébrale de 50%, non vertébral de 20 à 30%. L’ostéoporose reste une maladie sous-diagnostiquée et sous-traitée. Le but de cette étude est de connaître le devenir des patients une année après la survenue d’une fracture.
Méthode: Pendant une année, tous les patients de plus de 50 ans admis au CHUV pour une fracture ont été interviewés (données démographiques, type de traumatisme, traitement de l’ostéoporose, réalisation d’une densitométrie osseuse (DXA)). Les patients et leurs médecins-traitants ont reçu une information écrite sur l’opportunité d’effectuer un bilan et éventuellement un traitement de l’ostéoporose. Les patients ont été contactés téléphoniquement une année plus tard.
Résultats: Sur les 600 patients inclus (femmes 73%; âge moyen 74 ± 13 ans; fractures atraumatiques 84%, hospitalisation 79%), des informations ont été obtenues une année plus tard pour 356. 285 patients (80%) vivent à domicile, 23 (7%) en EMS et 46 (13%) sont décédés. 297 patients (73 ± 12 ans) ont répondu au questionnaire téléphonique. Le nombre de patients ayant eu une DXA a passé de 32 (11%) à 66 (22%). Le nombre de patients traités par calcium±vitamine D a passé de 83 (28%) à 129 (43%), et ceux sous bisphosphonates de 21 (7%) à 55 (19%). 23 patients (73 ± 12 ans) ont eu au moins une nouvelle fracture, atraumatique chez 22. Les sites de fractures étaient: hanche 30%, avant-bras 30%, squelette axial 13%, humérus 9%, tibia/péroné 9%. Le risque annuel de nouvelle fracture était plus élevé si la première fracture était typiquement ostéoporotique: 9% vs 3%. La proportion de patients traités était la même pour ceux ayant eu et ceux n’ayant pas eu de nouvelles fractures.
Conclusion: Chez les hommes et femmes de plus de 50 ans ayant présenté une fracture ostéoporotique, une DXA est rarement réalisée et un traitement spécifique de l’ostéoporose rarement initié. Le risque de nouvelle fracture à une année est relativement élevé, ce qui devrait d’autant plus motiver une prise en charge médicale agressive.

P58

Cardiac rehabilitation improves patients' risk factor awareness and risk perception

Merz K., Hoffmann A., Büchi S., Battegay E., Zimmerli L. (Basel, Zürich)

Objective: Most patients with coronary artery disease (CAD) have treatable atherogenic risk factors (RF) such as lipid abnormalities, hypertension, diabetes, and smoking. Adequate awareness of RF is a key first step that enables patients to address their risk factors. We hypothesised that RF awareness improves after a cardiac rehabilitation programme.
Design and method: A total of 90 patients (17 women and 73 men) aged 62 ± 11 years with CAD confirmed by coronary angiogram were assessed at the beginning and 65 of them at the end of a 12-week outpatient exercise-based comprehensive cardiac rehabilitation programme at the University Hospital Basel. Patients were asked to recall as many cardiac RFs as possible and to rate the risk of seven given RFs. For RF rating a visualisation technique, PRISM (Pictorial Representation of Illness and Self Measure), was used.
Results: The mean RF knowledge at the beginning of the rehabilitation programme was 4.2 ± 1.8 (median 4) out of a possible 12. Smoking (81%), excess stress (60%) and lack of exercise (48%) were the most common factors reported whereas the other well known RFs such as lipid abnormalities (48%), hypertension (29%) and diabetes (16%) were mentioned by a minority of patients. Patients affected by RFs did not recall them more often than patients without the corresponding RF. In patient-perceived risk of seven given RF, smoking was perceived to have the greatest risk, followed by hypertension, lipid abnormalities and excess stress. Family history of CAD was perceived as low risk by patients. After the rehabilitation programme RF knowledge improved to 5.2 ± 1.6 (median 5, $p < 0.001$); positive family history and cholesterol were perceived to have greater risk than at entry ($p = 0.03$ and $p = 0.06$, respectively).
Conclusions: Patients with CAD have limited knowledge about RFs of their disease, whether affected by them or not. In particular, knowledge about traditional RFs such as hypertension, diabetes and lipid abnormalities is low in general prompting. This is in contrast to the high patient-perceived risk of these RFs when they are specifically asked about them. A cardiac rehabilitation programme can improve RF knowledge and modify risk perception in patients. Therefore, high-risk patients, such as patients with CAD, should be specifically targeted with educational strategies in order to improve RF knowledge and behavioural modification.

P59

Histoire clinique: asystolie ictale lors d'une crise épileptique inaugurale

Pannatier M., Faucherre M., Hecker E., Hayoz D. (Fribourg)

Un patient de 69 ans, ayant pour seul antécédent neurologique un accident ischémique cérébral transitoire, présente, dans les suites d'une opération de résection vésicale transurétrale, 3 malaises avec mouvements toniques. L'enregistrement électroencéphalographique (EEG) a permis d'objectiver lors d'un malaise similaire des ondes alpha-thêta au niveau temporal gauche avec généralisation secondaire. Parallèlement, l'enregistrement électrocardiographique (ECG) simultané met en évidence, quelques secondes après le début de la crise épileptique, une asystolie de 23 secondes consécutives. Ce cas d'asystolie ictale a fait l'objet d'un consilium entre neurologues et cardiologues à l'issue duquel la décision d'implanter un pacemaker a été prise, compte tenu de la cardiopathie ischémique dont souffre le patient. Sous traitement d'acide valproïque, il n'a plus présenté de crise épileptique et se porte bien. Une base de données [1] ayant monitoré 6285 patients par enregistrement EEG-ECG-vidéo a relevé une incidence de 0,27% d'asystolie ictale. Sur les 10 cas, 8 sont survenus lors d'épilepsie temporale et 2 lors d'épilepsie extratemporale. Dans les 8 cas d'épilepsie temporale, les patients ont présenté une atonie soudaine de 42 secondes en moyenne, typique d'une hypoperfusion cérébrale, survenant à partir de périodes d'asystolie supérieures à
8 secondes. L'issue fatale possible de cette condition (Sudden Unexplained Death in Epilepsy, SUDEP) rend son dépistage et sa reconnaissance cruciaux. Ainsi, la survenue d'atonie, communément atypique lors d'épilepsie temporale se traduisant cliniquement par une chute ou une syncope tardive au cours d'une crise d'épilepsie typique doit faire rechercher une asystolie secondaire. Les options thérapeutiques sont à discuter de cas en cas, se limitant à un traitement médicamenteux adéquat pour les patients qui y répondent, à l'option plus radicale de l'implantation d'un pacemaker pour les cas de résistance pharmacologique ou les patients présentant un terrain préalable de cardiopathie. La physiopathologie sous-jacente a fait l'objet d'une autre étude qui postule comme cause de ces asystolies ictales une augmentation du tonus vagal médiée par l'effet parasympathique de la stimulation corticale de l'hémisphère gauche.
1 Neurology 2007;69:434–441.

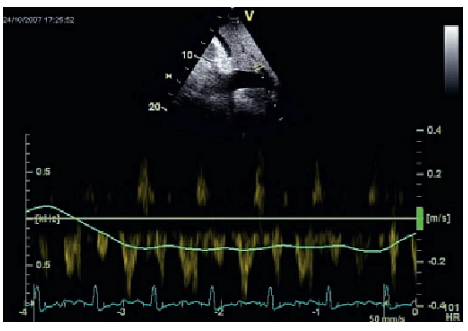
P60

Pericarditis constrictiva after cardiac surgery: a report of two cases

Stähli C., Moll C., Krause M., Widmer F. (Münsterlingen)

Introduction: During the last decades, the predominant cause of constrictive pericarditis shifted from infectious (eg tuberculous) to therapy-related aetiologies. Cardiac-surgery and radiotherapy account for most cases today. The constriction develops from pericardial effusion to fibro-elastic, subacute pericarditis which still may be reversible. When the disease progresses to a rigid, shell-like chronic pericarditis, only surgery may be successful. Echocardiography plays a pivotal role in the diagnosis of constrictive pericarditis, however, differentiation between constrictive and restrictive impairment may be difficult. We report two patients with rigid-shell constriction after cardiac surgery and the immediate hemodynamic normalization after surgical pericardectomy.
Patient 1: Male, age 80; 17 months after aortic valve replacement, he presented with relapsing bilateral pleural effusion, orthopnea and jugular vein distention (NYHA IV, BNP 284 ng/ml). There was no evidence of LV or valve dysfunction. Doppler studies revealed an expiratory increase of enddiastolic flow reversal in hepatic veins and a lack of respiration dependent variation of transmitral and transtricuspidal flow (Figure). The diagnosis of pericardial constriction was confirmed by catheterisation. A NSAR trial over 3 months did not improve the symptoms.
Patient 2: Male, age 62; two months after aortic valve replacement, he presented with dyspnea, anasarca and jugular vein distention (NYHA III, BNP 674 ng/ml). LV- and valve function were normal. Doppler studies showed an expiratory increase of enddiastolic flow reversal in hepatic veins. Cardiac catheterisation confirmed the diagnosis of pericarditis constrictiva. Impaired renal function forestalled drug therapy with NSAR.
Therapy: Both patients underwent surgical pericardectomy which resulted in immediate normalisation of hemodynamics and echo-doppler studies. Histologically, pericardial inflammation and fibrosis was found.
Comments: Cardiac impairment after successful cardiac surgery may be due to evolving pericardial constriction. Jugular vein distension, anasarka and characteristic doppler-echocardiography signs support the diagnosis of pericarditis constrictiva. An invasive confirmation of the diagnosis is mandatory. If the constrictive features do not resolve by NSAR, surgical pericardectomy is the therapy of choice.

Figure 1
Pericarditis



P61

Übelkeit und Erbrechen als Zeichen einer akuten Bronchoobstruktion bei ASS-Intoleranz

Dürr C., Michel S., Fricker M., Helbling A. (Bern)

Hintergrund: Die Inzidenz einer Aspirinintoleranz in der Allgemeinbevölkerung wird zwischen 0,6–2,5%, bei Asthmatikern bis zu 11% angegeben. Kontrollierte Provokationstestungen (inhalativ oder oral) mit Acetylsalicylsäure (ASS) oder nichtsteroidalen Antirheumatika (NSAR) sind das diagnostische Mittel der Wahl. Die Symptome einer ASS-Intoleranz sind mannigfaltig und reichen von akutem Bronchospasmus, akuter Urtikaria, Angioödem, Flushing, akuter Rhinitis oder Konjunktivitis über Myokardischämie bis zum anaphylaktischen Schock.
Kasuistik: Ein 42jähriger Patient mit chronisch obstruktiver Nasenatmungsbehinderung wurde uns zur Abklärung zugewiesen. Bereits zweimal wurde wegen rezidivierender Polyposis nasi ein operativer Eingriff durchgeführt, allerdings ohne anhaltenden Erfolg. Ein Asthma war nicht bekannt. Anamnestisch traten nach Einnahme von ASS/NSAR wiederholt Übelkeit, Erbrechen oder eine akute Urtikaria auf. Im Blutbild bestand keine Eosinophilie, das eNO (Niox) in der Ausatmungsluft war normal (<20 ppb), der Metacholinbronchoprovokationstest (>2,4 mg) wie auch der inhalative L-ASS-Provokationstest (>60 mg) fielen negativ aus. Daher wurde eine orale Provokationstestung mit ASS, beginnend mit 80 mg, durchgeführt. Bei der kumulativen Dosis von 240 mg ASS wurde ein Peakflow-Abfall (PEF) von 580 auf 470 l/min. verzeichnet. Der Patient beklagte keinerlei, insbesondere aber keine respiratorischen Beschwerden, so dass die Testung fortgeführt wurde. Nach kumulativ 400 mg ASS äusserte er plötzlich Übelkeit ohne respiratorische Symptome. Der PEF betrug 320 l/min. und eine Bradykardie von 54/min wurde festgestellt. Nach heftigem Erbrechen realisierte der Patient ein thorakales Engegefühl, das er dem Erbrechen zuordnete. Weil eine bronchiale Obstruktion offensichtlich war, wurde dem Patienten inhalativ Salbutamol und Adrenalin sowie peroral Levocetirizin und intravenös Methylprednisolon verabreicht, was zu einer raschen klinischen Besserung führte (PEF 550 l/Min).
Konklusion: Übelkeit und Erbrechen können einen akuten Bronchospasmus bei ASS-Intoleranz maskieren. Aufgrund der begleitenden Bradykardie, Nausea und akutem Erbrechen ist eine vagale Stimulation die wahrscheinlichste Erklärung dieser «gastro-bronchialen» Reaktion.

P62

«...dieses Antibiotikum macht Brustschmerz....»

Kröger A., Alfaré C., Bachmann U., Gubler C. (Uster)

Eine 83jährige Patientin wird mit akut aufgetretener Dyspnoe und rechtsthorakalen Schmerzen zugewiesen. In der konventionellen Röntgenaufnahme des Thorax zeigt sich eine Atelektase des rechten Unterlappens (Abb. 1). Bei klinischem Verdacht auf Lungenembolie wird ein CT des Thorax durchgeführt. Hier findet sich eine stenosierende Raumforderung im Bereich des rechten Unterlappens (Abb. 2). Eine Lungenembolie kann ausgeschlossen werden. Bei einem bekannten Nikotin-abusus steht der Verdacht auf ein malignes Geschehen im Raum. Zur weiteren Abklärung wird eine Bronchoskopie durchgeführt. Hier sieht man eine den Bronchus intermedius verlegende Tablette (Abb. 3), welche in gleicher Sitzung via Bronchoskop entfernt werden kann. Nach erneutem Befragen der Patientin stellt sich heraus, dass die Beschwerden unmittelbar nach Einnahme eines Antibiotikums wegen eines Harnwegsinfektes aufgetreten waren. Es war offensichtlich zu einer Aspiration der Tablette gekommen. Retrospektiv betrachtet, handelte sich bei dem Tumor «nur» um eine aspirierte Tablette (Abb. 4), deren Einnahme eigentlich einen kurativen Zweck hatte. Nach antibiotischer, symptomatischer und physio-therapeutischer Therapie der durch Tabletten-Aspiration verursachten poststenotischen Pneumonie und Unterlappenatelektase, kommt es innerhalb von 2 Wochen zur Genesung der Patientin Die Verlaufsbronchoskopie zeigt einen unauffälligen Befund. Fremdkörperaspirationen sind bei Kindern nicht so selten und werden differentialdiagnostisch bei der Abklärung von Atelektasen in Betracht gezogen [1]. Typischerweise ist die Anamnese bland und die Kinder 3–10 Jahre alt [2]. Bei Erwachsenen ist die Fremdkörperextraktion eine Seltenheit; weniger als 1% aller Bronchoskopien werden wegen einem Fremdkörper indiziert [3]. Die Diagnose kann mit der Computertomographie idealerweise als virtuelle 3D Rekonstruktion gestellt werden [4], eine Missinterpretation als endoluminaler Tumor ist allerdings nicht selten [5]. Fremdkörper sind meist Essensbestandteile (Knochen) und Zahnimplantatteile oder Zähne [6]. Therapie der Wahl ist die flexible bronchoskopische Entfernung, die in 99% gelingt [7]. Dieser Fall unterstreicht die Wichtigkeit einer genauen Anamneseerhebung. Die Patientin war nicht überrascht vom Bronchoskopiebefund: «..ich habe doch gesagt, dieses Antibiotikum ist schuld an diesen Brustschmerzen …».
Referenzen
1 Int J Pediatr Otorhinolaryngol 2007 Feb;71(2):241–6.
2 Eur J Cardiothorac Surg. 2005 Sep;28(3):369–74
3 Eur Respir J. 1999 Oct;14(4):792–5.
4 Semi Ultrasound CT MR 2005 Oct;26(5):364–73
5 Respiration 2006;73(6):826–9
6 Pneumologie 2005 Mar;59(3):174–7.
7 Ann Saud Med 2006 Jul-Aug;26(4):283–7

P63

Die Behandlung eines 24jährigen Patienten mit fortgeschrittener, kavernöseer multiresistenter Lungentuberkulose

Sladovnik P., Shang Meier H., Rossi M., Pfyffer G.E., Karrer W. (Crans-Montana, Luzern)

Einleitung: Anfang 2007 reiste der 24jährige Asylsuchende aus der Elfenbeinküste in die Schweiz (CH), um seine Tuberkulose (TB) behandeln zu lassen. In seinem Heimatland wurde die Behandlung wegen Mangel an Medikamenten wiederholt unterbrochen, was zu Resistenzproblemen führte. Seit 2005 wird in der CH bei Asylsuchenden kein TB-Screening mehr durchgeführt. Jedoch findet ein Interview durch ausgebildete Pflegefachkräfte statt [1]. Der Patient wurde in ein lokales Spital eingewiesen.
Methoden: Die Behandlung erfolgte mit Isoniazid (INH), Rifampizin (RMP), Ethambutol (EMB) und Pyrazinamid (PZA), ergänzt wegen vermuteter Resistenz mit Amikacin. Aufgrund der Resistenzprüfung wurde eine ausgedehnt resistente TB (Extensively Drug Resistant TB XDR-TB) diagnostiziert. Bis heute registrierte man in der CH keine XDR-TB. Nach 10 Wochen stationärer Therapie wurde das Sputum direkt negativ und der Patient ohne weitere Kontrollmassnahmen in eine Asylantenunterkunft nach Luzern verlegt. Erst mit erneut mikroskopisch positivem Sputum wies ihn der zugezogene Heimarzt sofort ins Luzerner Kantonsspital (LUKS) ein, von wo er anschliesend zur Behandlung in die Luzerner Höhenklinik Montana verlegt wurde.
Resultate: Die Resistenzprüfung im LUKS ergab Empfindlichkeit auf EMB, Moxifloxacin (MFX) und Amikacin (AMK), was nach internationalen Richtlinien einer multiresistenten TB (Multi Drug Resistant TB MDR-TB) entspricht, mit einer deutlich besseren Prognose. Das Resistenzmuster zeigte, dass eine Behandlung nur noch mit INH, EMB, AMK, MFX und Linezolid möglich war. Nach 9 Wochen konnte eine Lobektomie des linken Oberlappens durchgeführt werden um die Masse des Infektionsherdes zu verkleinern. Nach 5 Monaten Behandlung wurden aufgrund mehrfach negativer Sputumkulturen und schwerwiegender Nebenwirkungen (Ototoxizität, Polyneuropathie) AMK und Linezolid sistiert. Die Behandlung mit INH, EMB und MFX wird 1 Jahr weitergeführt.
Schlussfolgerung: 1. Ungenügende Medikation führte zur MDR-TB. 2. Die MDR-TB hat in Entwicklungsländern eine schlechte Prognose. 3. Die XDR-TB hat auch in westlichen Ländern eine sehr schlechte Prognose, welche sich derjenigen der Vor-Tuberkulostatika Ära annähert. Deshalb ist eine genaue Einteilung aufgrund des Resistenzmusters prognostisch entscheidend.
(1) Mathez Ch et al. Active screening for pulmonary tuberculosis by chest x-ray among immigrants at the Swiss border. Swiss Med Wkly. 2007;137:649–654.

Abbildung 1
Multiresistente, kavernöse Lungentuberkulose

Abbildung 2
Lungentuberkulose.
St.n. Oberlapenresektion links

P64

Piqûre d'insect aux urgences: toujours une banalité?

Lepori M., Kistler M. (Bellinzona)

Background: Les piqûres d'insectes sont une cause fréquentes de consultations en urgences pendant les mois d'été. Leur prise en charge n'est pas standardisée et les données de la littérature sont rares en dehors de ceux concernant la prise en charge des anaphylaxies graves.
Buts: Analyser l'incidence, les modalités de prise en charge et l'évolution clinique des patients consultant un centre d'urgences pluridisciplinaire, à la suite d'une piqûre d'insecte.
Methodes: Analyse prospective par formulaire standard, sans directives diagnostique ou thérapeutiques, des cas entre le 1er juin et le 31 août 2006.
Resultats: Pendant la période d'observation nous avons enregistré 128 cas (3,5% des consultations): Seulement 4 patient avaient une anamnèse d'allergie aux hyménoptères. Un seul patient utilisait une protection anti-insectes au moment de la piqûre. Le nombre de patients avec réaction systémique était de 19 (20%) et le nombre d'hospitalisation (>24 heures) de 13 (10%). Trois patients ont été hospitalisé en Soins Intensifs avec un choc anaphylactique. 109 patients présentaient uniquement une réaction locale dont 16% avaient en plus des signes de surinfection (lymphangite, adénopathie satellite ou signes d'abcédassions). Plus de 70% des patients ont reçu des anti-H1, 47% des stéroïdes, 35% des antibiotiques et 12% un rappel antitétanique. Malgré 22 cas de piqûre par tique aucune prophylaxie par doxycicline à été proposée. Un seul cas d'erythema migrans a été observé .
Conclusions: 1 La piqûre d'insecte est un motifs de consultation fréquent pendant l'été. 2. Les cas graves avec manifestations systémiques nécessitant une hospitalisation ne sont pas rares, et ne sont pas strictement liés à un' anamnèse préalable d'allergie. 3. La prise en charge de ces patients est très hétérogène et l'utilisation de certains traitements, en particulier les antibiotiques les stéroïdes et le rappel antitétanique, est probablement exagérée. 4. Une plus grande utilisations par les patients de moyens de protection contre les insectes pourrait diminuer la fréquence des cas

---

P65

Characteristics of bleeding complications in patients with anticoagulant treatment

Rothschild S., Seifert B., Conen D. (Aarau, Zürich)

Background/Aims: Anticoagulation treatment is effective in the prevention of stroke as well as deep venous thrombosis (DVT) and pulmonary embolism (PE). Its preventive benefit is to balance against possible bleeding complications. We sought to assess risk factors for the severity of bleeding events in patients under anticoagulant treatment.
Methods and patients: Clinical characteristics, type of anticoagulant treatment, bleeding site, risk factors, and additional drugs taken by patients were analysed in 87 bleeding complications during an observation period of 12 months.
Results: Eighty-seven bleeding complications in 84 patients (mean age, 79 years; 51% female) were observed from January to December 2005 at the Department of Internal Medicine at the Cantonal Hospital of Aargau. Most bleeding complications occurred in the gastrointestinal tract (54%). The median time interval from the beginning of the anticoagulant treatment to the bleeding event was 34 months. Forty-nine percent of events occurred after a treatment time above 36 months. Age was not found to influence the severity of bleeding but the duration of anticoagulant treatment before the occurrence of a complication was significantly longer for older patients ($p = 0.001$).
Conclusions: Our study shows no influence of age on severity of bleeding complications. Furthermore in patients with advanced age complications occurred later in the treatment course than in younger patients. Overall we assessed many bleeding events in patients treated for over three years. Therefore we emphasize to closely control patients with anticoagulant treatment also in the later course of treatment and to mind the anticoagulation when order new drugs.

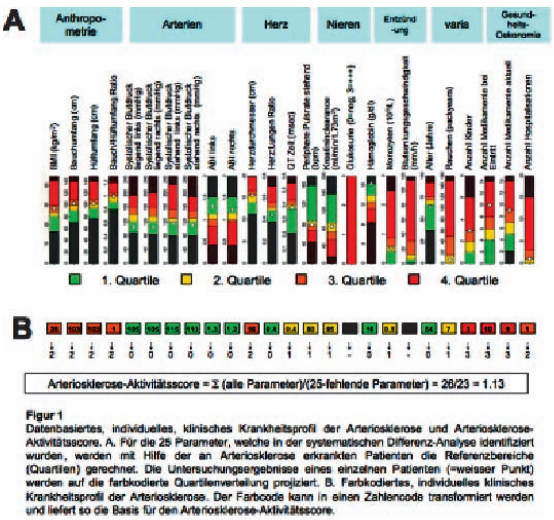
P66

«BRUDABAK» oder: Wie die sorgfältige, ärztliche Untersuchung Mehrwert generiert

Biedermann B.C. (Bruderholz)

Im Zeitalter modernster Medizintechnologie und molekularer, komprehensiver Untersuchungsverfahren (den sogenannten «-omics») droht die ärztliche Untersuchung, d.h. die Anamnese, der Status und einfache Zusatzabklärungen (Thoraxröntgenbild, EKG, Labortests), mehr und mehr vernachlässigt zu werden. Dennoch bildet sie immer noch den unmittelbarsten Zugang zur Krankheit eines Patienten. Es stellt sich die Frage, wie präzise diese Untersuchungsmittel Krankheiten wirklich erfassen können. Am Beispiel der häufigen Krankheit «Arteriosklerose» wurde geprüft, ob mit Hilfe einer umfassenden, standardisierten internistisch-ärztlichen Untersuchung diese Krankheit bei hospitalisierten Patienten zuverlässig diagnostiziert werden kann. Wenn Daten der ärztlichen Untersuchung nach den Regeln der Differenz-Analyse verarbeitet werden, kann einerseits ein patientenbezogenes, individuelles klinisches Krankheitsprofil für die Arteriosklerose hergeleitet und andererseits für jeden Patienten ein Arteriosklerose-Aktivitätsscore bestimmt werden. Dieser Aktivitätsscore ist verglichen mit der konventionellen, kardiovaskulären Risikoeinschätzung oder mit modernen Biomarkern mindestens gleichwertig als Diagnoseverfahren. Mit Hilfe des klinischen Krankheitsarrays lassen sich Untergruppen systematisch vergleichen und objektive Klassifizierungskriterien erkennen. So zeigen sich beispielsweise signifikant unterschiedliche Phänotypen bei Patienten mit koronarer Herzkrankheit, zerebrovaskulärer Insuffizienz oder peripher arterieller Verschlusskrankheit. Auch der Phänotyp von Männern und Frauen mit symptomatischer Arteriosklerose, d.h. mit einer Arteriosklerose, die sich durch kardiovaskuläre Ereignisse manifestiert, zeigt teils erwartete, teils unerwartete Unterschiede. Schliesslich identifiziert der klinische Korrelationsplot Krankheitszustände, die mit der symptomatischen Arteriosklerose assoziiert sind (zum Beispiel die Osteoporose). Mit Hilfe eines IT-basierten Erfassungsinstrumentes für klinische Daten können individuelle Krankheitsprofile, der Krankheitsaktivitäts-Score, Krankheitsarrays, oder Korrelationsplots für definierte, häufige Krankheiten zeitverzugslos und für eine ökogeographisch relevante Patientenpopulation erstellt werden. Diese Technik basiert auf erschwinglichen, verfügbaren oder bereits vorhandenen, empirischen Daten und visualisiert komplexe, medizinische Zusammenhänge auf eine intuitiv nachvollziehbare Weise.

Abbildung 1
Krankheitsprofil und Aktivitätsscore der Arteriosklerose



Figur 1
Datenbasiertes, individuelles, klinisches Krankheitsprofil der Arteriosklerose und Arteriosklerose-Aktivitätsscore. A. Für die 25 Parameter, welche in der systematischen Differenz-Analyse identifiziert wurden, werden mit Hilfe der an Arteriosklerose erkrankten Patienten die Referenzbereiche (Quartilen) gerechnet. Die Untersuchungsergebnisse eines einzelnen Patienten (=weisser Punkt) werden auf die farbkodierte Quartilenverteilung projiziert. B. Farbkodiertes, individuelles klinisches Krankheitsprofil der Arteriosklerose. Der Farbcode kann in einen Zahlencode transformiert werden und liefert so die Basis für den Arteriosklerose-Aktivitätsscore.

P67

Triptane & Troponin

Weder C., Schneemann M. (Zürich)

Eine 67jährige Patientin wurde uns wegen Thoraxschmerzen notfallmässig zugewiesen. In der persönlichen Anamnese der Patientin war eine Migräne bekannt, welche unter einer Bedarfsmedikation mit Naratriptan befriedigend eingestellt war. Die Patientin hatte am Vorabend des Spitaleintritts unter einer akuten Migräneattacke mit Kopfschmerzen und Übelkeit gelitten und daraufhin wie gewohnt 2,5 mg Naratriptan eingenommen. Darunter klangen die Kopfschmerzen ab. 30–60 Minuten nach der Naratriptan- Einnahme verspürte die Patientin erstmalig Thoraxschmerzen. Die Schmerzen nahmen im Verlauf der folgenden Nacht zu und strahlten in den Hals aus. Die Patientin stellte sich am Morgen bei ihrer Hausärztin vor, welche die Patientin mit einem akuten Koronarsyndrom bei elektrokardiographisch T-Wellen-Inversion über der Vorderwand und erhöhtem Troponin ans Universitätsspital Zürich zuwies. Im Eintritts- EKG waren die T- Wellen über der Vorderwand invertiert, die CK lag bei 518U/l (Norm <167U/l) und das Troponin bei 0,42 ug/l (Norm <0,1 ug/l). In der Koronarangiographie kamen normalkalibrige, glattwandige Koronararterien zur Darstellung. Die Ventrikulographie ergab eine EF von 59%. Somit gingen wir als Ursache des akuten Koronarsyndroms von einem Koronarspasmus unter Naratriptan aus. Triptane haben sich in der Anfallsbehandlung der Migräne etabliert. Sie führen durch Aktivierung der $5HT_{1B/1D}$-Rezeptoren zu einer Vasokonstriktion der bei einem Migräneanfall erweiterten zerebralen Blutgefäße. Zudem hemmen sie die Ausschüttung vasoaktiver Peptide und vermindern die Ausbreitung von Schmerzreizen über die Hirnrinde. Obwohl Triptane ihre Wirkung vor allem an den zerebralen Blutgefässen entfalten, wurden auch koronar, pulmonal und systemisch Vasokonstriktion beschrieben. Unter Triptanen treten zwar häufig (1–7%) Thoraxschmerzen auf, welche aber meist transient, mild und ohne ischämisches Korrelat sind. Die Häufigkeit von Myokardinfarkten unter Triptanen wird als sehr gering eingeschätzt. Der Grossteil der publizierten Fallberichte betrifft das Auftreten von Myokardinfarkten unter Sumatriptan, wobei angiographisch sowohl stenosierte wie auch normalkalibrige Koronararterien nachgewiesen wurden. Nebst Sumatriptan ist das Auftreten von Myokardinfarkten unter Zolmitriptan beschrieben. Triptane sollten bei bekannter koronarer Herzkrankheit nicht verschrieben werden. Heftige, nicht nachlassende Thoraxschmerzen unter Triptanen sind abklärungsbedürftig.

P68

Ambulances et SMUR en cas d'urgences vitales au cabinet médical: implications pour la formation et l'équipement du médecin de premier recours

Potin M., Pittet V., Staeger P., Vallotton L., Burnand B., Yersin B. (Lausanne)

Introduction: Tout praticien est confronté quotidiennement à des urgences. Parmi celles-ci, les urgences vitales peuvent avoir des conséquences majeures pour le patient et pour le praticien. Le but de cette analyse est de déterminer la fréquence de survenue des urgences vitales au cabinet médical qui motivent l'intervention d'une ambulance, avec ou sans médicalisation par un SMUR (Service Mobile d'Urgence et de Réanimation) et d'en évaluer des conséquences en terme de mise en place de procédures, d'équipements ainsi que de formations post-graduée ou continue spécifiques.
Matériel et méthode: Etude rétrospective des fiches d'intervention pré-hospitalière des services d'ambulances et des missions des SMUR du canton de Vaud (650'000 habitants) entre 2003 et 2006 pour les missions dont la prise en charge d'un patient a eu lieu dans le cadre d'un cabinet médical.
Résultats: Entre 2003 et 2006, 2'224 interventions avec ambulances ont eu lieu dans un des 1'655 cabinet médical vaudois (= 2,3% de l'ensemble des missions) et, dans >90% des cas, dans un délai de 20 minutes. Parmi les interventions, on relève les urgences suivantes (n =, % des interventions): cardio-vasculaires: 755 (= 33,9%), dont 17 arrêts cardio-respiratoires (ACR); respiratoires: 165 (= 7,4%); neurologiques: 138 (= 6,2%); psychiatriques: 129 (= 5,8%); traumatologiques: 475 (= 21,4%), dont 261 (= 54,9%) concernent les extrémités; diverses: 205 (= 9,5%); autres: 359 (= 16,1%). Sur ces interventions, 634 (= 28,5%) ont bénéficié d'une médicalisation par un SMUR, dont 440 (= 70% des missions SMUR au cabinet) pour des urgences cardio-vasculaires. Il y a eu 6 cas de décès au cabinet.
Discussion: Les urgences cardio-vasculaires au cabinet représentent un tiers des interventions faisant appel à une ambulance, mais plus des deux tiers des interventions nécessitant une médicalisation, soit plus que pour les autres sites d'interventions médicalisées dans la communauté (46%).
Conclusions: Les urgences vitales au cabinet médical ne sont pas négligeable, peuvent avoir des conséquences lourdes (ACR, décès) et perturber significativement son fonctionnement. Dès lors, une formation appropriée tant pour le médecin que pour son personnel, ainsi qu'un équipement adéquat (par ex. salle équipée avec défibrillateur, appareil d'aérosol, attelles pour les extrémités) devraient être encouragés et généralisés auprès du corps médical.

P69

La maladie de Creutzfeldt-Jakob sporadique: présentation clinique et diagnostique

Truong M.H., Ruffieux A., Hayoz D., Betticher D. (Fribourg)

Introduction: La maladie de Creutzfeldt-Jakob est une maladie infectieuse rare du système nerveux central. La forme sporadique, la plus fréquente (85%), se manifeste par une démence et des troubles neurologiques diffus d'évolution rapide sur quelques mois. L'issue est fatale dans tous les cas.
Cas clinique: Une femme de 61 ans présente des troubles mnésiques de survenue rapide. Le MMS est à 19/30 et le test de l'horloge à 2/7points. Le bilan étiologique de routine de la démence est normal. L'évolution clinique est rapide avec apparition d'une aphasie, d'un parkinsonisme, d'une ataxie à la marche et de myoclonies diffuses. L'EEG met en évidence des complexes triphasiques pseudo-périodiques. L'IRM cérébrale avec séquences de diffusion objective un hypersignal sous forme de ruban cortical et au niveau de la tête des noyaux caudés et des putamens prédominant à droite. L'analyse du liquide céphalo-rachidien ramène des traces de la protéine 14-3-3. Sur la base de ces résultats, nous suspectons une maladie de Creutzfeld-Jakob sporadique. La patiente décèdera neuf mois après le début des symptômes. L'examen anatomo-pathologique confirmera le diagnostic par la spongiose, gliose, perte neuronale et présence de la protéine prion anormale au niveau du cortex, des noyaux gris centraux et du thalamus,
Description: La maladie de Creutzfeldt-Jakob sporadique touche des patients entre 50–70 ans et se manifeste par une démence précoce avec des symptômes peu spécifiques au début de la maladie (troubles de la personnalité, du sommeil, psychiatriques, visuels), d'où la difficulté de poser un diagnostic de certitude. L'évolution est rapidement progressive avec l'apparition de symptômes plus spéficiques (myoclonies, ataxie, signes pyramidaux et extra-pyramidaux, cécité corticale et mutisme akinétique).
Diagnostic: Le diagnostic probable est basé sur la clinique, la présence de la protéine 14-3-3 dans le liquide céphalo-rachidien et les lésions caractéristiques à l'EEG (complexes triphasiques, périodiques et généralisés) et à l'IRM (hypersignal sous forme de ruban cortical et au niveau des noyaux caudés et putamens). Le diagnostic définitif repose sur les résultats de l'examen anatomo-pathologique (gliose, spongiose, perte neuronale et présence de la protéine prion anormale).

P70

Fortuite discovery of a right atrium mass

Zaugg D., Jaussi A. (Lausanne)

During performing a transthoracic echocardiography (TTE) to evaluate left ventricular function and follow-up of a moderately severe calcified aortic valvular stenosis to a 55-years old smoker known for a metabolic syndrom, who has had a myocardial infarction at 40, a right atrium (RA) mass was incidentally found by the cardiologist. The mass was highly mobile prolabing in the right ventricule and in contiguity with a mass of low echodensity in the inferior vena cava (IVC) where an accelerated flow was documented. The biological results showed a polycythemia with hemoglobin (Hb) to 200g/l, an hematocrit (Ht) to 59%, erythropoietin (EPO) was elevated to 41 U/l

(5–25 U/l), as well as interleukin-6 (Il-6) to 48.6 pg/l (<0.3 pg/ml) and alpha-foetoprotein (AFP) >12'000kU/l (<0.5 kU/l). Those values associated with IVC and RA mass pointed first to a renal cell carcinoma, but a CT-scan showed a huge hepatic mass, also objectivated at abdominal ultrasound examination, corroborating the diagnosis of hepatocellular carcinoma (HCC). A case control study from the USA demonstrated that an alcohol exposure of >1500 g-years, tobacco >20 pack-years, a body mass index >30 Kg/m^2, and patients with diabetes mellitus were independent risk factors for HCC. During a clinical course of HCC, patients may develop several paraneoplasic syndromes such as hypoglycemia, hypercholesterolemia, hypocalcaemia and erythrocytosis. The incidence of erythrocytosis is highest in renal cell carcinoma, rather low in HCC. It seems to be linked with high level of AFP, large tumour and poor prognosis. This report represents the discovery of a RA mass while performing a TTE to evaluate left ventricular function and follow-up of a moderately severe calcified aortic valvular stenosis. The biological elevations of Hb, EPO, Il-6 was reminiscent of a renal cell carcinoma. However CT-scan and abdominal ultrasound established the diagnosis of HCC. This case confirms that TTE is a sensitive examination for the diagnosis of RA mass. Secondly, we should consider that patients with risk factors should be controlled for HCC, by performing hepatic ultrasound and AFP. Furthermore, understanding the mechanism of HCC growth and angiogenesis could improve the survival time of patients with HCC.

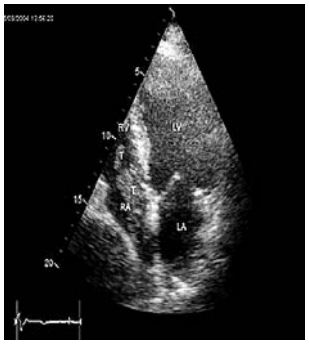


Figure 1
RA mass

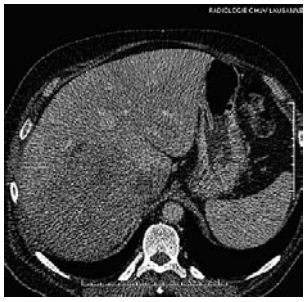


Figure 2
A huge hepatic mass

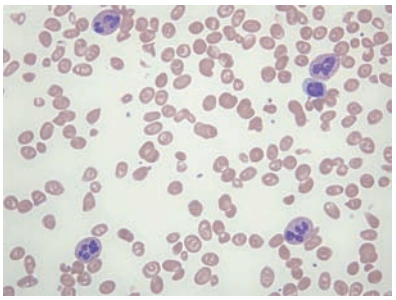
P71

From sore tongue to pancytopenia

Chapuis T., Favrat B., Bodenmann P. (Lausanne)

Objectives: Recognize non-neurological signs of cobalamin (vitamin B12) deficiency, identify hematological findings and establish diagnosis and treatment for pernicious anaemia.
Case: A 52-year-old man native to the Congo presented to the emergency ward after 14 days of shortness of breath and a sore tongue. He had no cough or fever, and no relevant information in his medical history. The physical examination was unremarkable.
Clinical Course: A chest X-ray and a full blood count were ordered. The chest X-ray was normal. The full blood count showed pancytopenia: the hemoglobin was 75 g/L with a MCV of 107fl, and the absolute reticulocyte count was 31 G/L. The WBC was 3.6 G/L, with 27% neutrophils, 63% lymphocytes and 96 G/L platelets. The peripheral blood smear (figure 1) revealed anisocytosis and hypersegmented neutrophils. The findings were low cobalamin (52 pmol/L; 133-675) and folate (4.2 nmol/L; >6.8) levels, and high homocysteine (101 mmol/L; 5-15) and methylmalonate (1.12 mmol/L; <0.28) levels. Iron, ferritin levels were normal, as were the other findings. A gastroscopy with biopsy showed atrophic gastritis. Anti-parietal cell and anti-intrinsic factor antibodies were positive. Cobalamin (1000 mcg i.m.) was given daily for 7 days, then every week for 4 weeks and then maintained at 1000 mcg every month. Daily folate was also given. Correction of the deficiencies led to a reticulocytosis (200 G/L) 10 days later. Six months later, the patient was asymptomatic and the peripheral blood smear was normal. Cobalamin, folate, methylmalonate and homocysteine levels were normal.
Discussion: The differential diagnosis of pancytopenia included cobalamin and folate deficiency, hyperslenism, myeloproliferative disorders, hypothyroidism, HIV. Pernicious anaemia was our leading diagnosis. Our patient developed non-neurological symptoms and a sore tongue without glossitis that was reversible after treatment. Rare hematological abnormalities included pancytopenia. Cobalamin deficiency can arise due to nutrition (e.g. vegans), malabsorption syndrome (e.g. pernicious anaemia) or from other gastrointestinal causes (e.g. bacterial overgrowth syndrome). The diagnosis is based on a low cobalamin level, but elevated methylmalonate and homocysteine levels are more sensitive diagnostics than is low serum cobalamin. Patients with pernicious anaemia have anti-intrinsic factor and anti-parietal cell antibodies. Treatment is intramuscular or oral and lasts a lifetime.

Figure 1: peripheral blood smear



P72

Subclaviathrombose auf der Grundlage eines ovariellen Hyperstimulationssyndroms (OHSS)

Keller C., Ballmer P. E. (Winterthur)

Fallpräsentation: Eine 32jährige Patientin wurde zur Abklärung linksseitiger Nackenschmerzen mit progredienter Schwellung supraclaviculär links zugewiesen. Die Patientin befand sich nach einer in vitro-Fertilisation (IVF) in der 8. Schwangerschaftswoche und war 4 Wochen zuvor wegen eines OHSS mit Pleuraerguss, Aszites und zystischen Ovarien hospitalisiert. In der klinischen Untersuchung zeigte sich eine 10x10 cm grosse, dolente und livide Schwellung supraclaviculär links mit Umgehungskreislauf bei sonst unauffälligem Status. Ausser einer Leukozytose (23,0x10^9/l) und einer Erhöhung des CRP (44 mg/l) bestanden keine Laborauffälligkeiten. Duplexsonografisch konnte eine Thrombose der V. subclavia und jugularis interna links bestätigt werden. In der MRI zeigte sich neben der Subclaviathrombose eine ausgedehnte, hyperintense Infiltration der umliegenden Weichteilstrukturen.
Diagnose, Therapie und Verlauf: Wir stellten nach Ausschluss anderweitiger Ursachen die Diagnose einer Thrombose der V. subclavia und jugularis links mit ausgeprägtem Weichteilödem auf der Basis eines OHSS Grad III, und verabreichten therapeutisch Fragmin®. Nach erfreulichem klinischem Verlauf konnte die Patientin nach 1 Woche entlassen werden.
Diskussion: Das OHSS wird in der Regel durch exogen zugeführte Hormone im Rahmen einer IVF ausgelöst. Milde Formen wurden auch im Zusammenhang mit Hypothyreose oder polyzystischem Ovarsyndrom beschrieben. Die Klinik des OHSS ist geprägt durch eine Vergrösserung der Ovarien mit Zystenbildung infolge Stimulation einer übermässigen Follikelanzahl und durch gesteigerte Kapillarpermeabilität mit Extravasation. In Abhängigkeit der Ovargrösse, der Klinik und der Oestrogenkonzentration werden 3 Schweregrade unterschieden. Normalerweise ist das OHSS innerhalb von 10 bis 14 Tagen spontan regredient, kann aber zu Komplikationen wie hypovolämischem Schock, Nierenversagen und ARDS führen. Thromboembolische Komplikationen im Bereich der V. axillaris bis jugularis und der Mesenterialgefässe, welche im Rahmen eines OHSS unabhängig von einer Thrombophilie 7–10 Wochen nach IVF auftraten, wurden beschrieben. Die Therapie beschränkt sich auf ein symptomorientiertes Vorgehen, im Falle einer Thrombose auf die Anwendung von Heparinen.

P73

Multidisziplinäres Management nach totaler Dünndarmresektion

Keller C., Rühlin M., Müller Ch., Haller A., Jaeggi M., Ballmer P.E., Imoberdorf R. (Winterthur)

Hintergrund: Ein Langzeitüberleben nach totaler Dünndarmresektion ist seit Etablierung der totalen parenteralen Ernährung (TPE) möglich. Diese ist mit hoher Morbidität und grosser psychischer Belastung assoziiert, was eine umfassende, multidisziplinäre Betreuung des Patienten voraussetzt.
Fallbeschreibung: Aufgrund einer akuten Mesenterialischämie wurde bei einem 44jährigen Mann eine totale Dünndarmresektion und Hemikolektomie rechts (mit Blindverschluss) durchgeführt. Die Ursachensuche mittels Holter-EKG, Echokardiografie, Vaskulitisscreening (ANA, ANCA, anti-native-DNA, anti-mitochondriale-AK, TPHA-Test) und Bestimmung der Antikardiolipin-Antikörper blieb erfolglos. Die TPE wurde mit Nutriflex lipid peri® (Braun Medical, Switzerland), Polyvitaminen, Spurenelementen und Flüssigkeit via Porth-à-cath mit 8 Stunden Verabreichungspause pro Tag eingestellt. Zur Drainage der Sekrete des oberen Gastrointestinaltraktes wurde eine PEG-Sonde implantiert. Unter intensiver Schulung durch eine Ernährungsberaterin und Homecarespezialistin erlernte der Patient die korrekte Handhabung der TPE. Regelmässige Nachkontrollen ergaben ein stabiles Körpergewicht im Normbereich (BMI 22 kg/m^2) ohne Anzeichen einer Malnutrition oder Störung des Hydratationszustandes. Ein Anstieg der Cholestasewerte auf ein im weiteren Verlauf stabiles Niveau (GGT 204 U/l, Referenzbereich (RB) 11–50 U/l; AP 293 U/l, RB 45–122 U/l) bei konstanter, milder Erhöhung der Transaminasen (GOT 45 U/l, GPT 81 U/l; RB: <40 U/l) und sonografisch leichter Steatose führten wir auf die TPE zurück. Trotz erfreulichem klinischem Verlauf und eingehender Aufklärung über die Risiken einer Dünndarmtransplantation konnte die psychische Belastung des Patienten mit zunehmender Depression und intensivem Wunsch nach einem Transplantationsverfahren kaum beeinflusst werden. Deshalb erfolgte die Anmeldung an die Transplantationssprechstunde des USZ.
Diskussion: Aufgrund ungenügender Erfahrung hinsichtlich Dünndarmtransplantation ist nach einer totalen Dünndarmresektion die TPE die Therapie der ersten Wahl, obwohl diese mit schweren Komplikationen wie Leberversagen, katheterassoziierten Infektionen und Stoffwechselstörungen assoziiert sein kann. Eine Transplantation kommt gemäss den internationalen Richtlinien nur nach Versagen der TPE in Frage, wobei letzteres allein durch die psychische Entwicklung des Patienten bedingt sein kann.

P74

Management of fragility fractures in Switzerland: a prospective study

Lamy O., Suhn N., Lippuner K. (Lausanne, Basel, Bern)

Introduction: There is a worldwide consensus that patients aged 50 years and older presenting with a fragility fracture should undergo diagnostic workup for osteoporosis. They benefit from measures aiming at reducing the risk for further fractures. Recent studies suggest that osteoporosis remains generally underdiagnosed and undertreated. A nationwide survey was conducted to assess the quality level of osteoporosis management in patients >50 years presenting with a fragility fracture to the emergency ward.
Methods: During a timeframe ranging from 8 to 16 months, all consecutive patients >50 years presenting with a fracture to the emergency ward in eight hospitals (Basel, Bern, Estavayer, Fribourg, Lausanne, Luzern, Riaz, Sankt-Gallen) were recruited between 2004 and 2006. Of the 4966 consecutive male (N = 1368, mean age 69.0 years) and female (N = 3598, mean age 73.9 years), 3667 were considered as having 3897 fragility fractures and included in the survey.
Results: The included patients presented with a fracture of the upper limbs (30.7%), the lower limbs (26.4%), the axial skeleton (19.5%) or at another localization, including malleolar fractures (23.4%). 1185 patients (data available for 3099 patients, 38.5%) reported one or more anamnestic fractures during adulthood. The average length of stay of the 2941 (80.2%) hospitalized patients was 9.0 ± 7.0 days. Only 49.8% returned home after discharge, 32.7% went to a rehabilitation clinic, 17.1% went to a nursing home or were transferred to another hospital, and 0.4% died. DXA measurement was available for 1152 (31.4%) patients. Of those 46.0% had an osteoporosis and 35.1% an osteopenia. The mean of the lowest T-score values was –2.34 in women and –2.16 in men. The treatment rate with a bone active substance alone or in combination with calcium and/or vitamin D supplements increased from 11.4% to 23.8% after fracture in women and from 4.7% to 13.8% in men.
Conclusion: In patients aged 50 years and older presenting with a fragility fracture osteoporosis remains underdiagnosed and undertreated in Switzerland.

P75

Obstruktives Schlafapnoesyndrom – gebessert nach Therapie einer Akromegalie

Fausch K., Jeker R., Kuhn M., Reinhart W. H. (Chur)

Fallbeschreibung: Bei einer 68jährigen Patientin wurde 2005 im Rahmen einer Abklärung eines chronischen Schmerzsyndroms die Diagnose einer Akromegalie gestellt. Der Insulin like growth factor (IGF) betrug 985 ng/ml (Normwerte: 100–300 ng/ml), das Growth Hormone (GH) war mit oraler Glucosebelastung nicht supprimierbar. Fremdanamnestisch bestand bei der Patientin Schnarchen und nächtliche Apnoephasen, klinisch fiel unter anderem eine Makroglossie auf. In der respiratorischen Polygraphie zeigte sich das Bild eines mittelschweren obstruktiven Schlafapnoesyndroms (OSAS) mit einem Apnoe-/Hypopnoe-Index von 30/Stunde, es kam zu massiven Entsättigungen (transkutane Sauerstoffsättigung <60%). Nach Therapie der Akromegalie mittels Entfernung eines Mikroadenoms in der Hypophyse persistierte weiterhin ein nächtliches Schnarchen, jedoch wurden fremdanamnestisch keine Atempausen mehr beobachtet. Die Tagesmüdigkeit besserte sich deutlich. Eine respiratorische Polygraphie bestätigte die Verbesserung des OSAS: Der Apnoe-/Hypopnoe-Index sank auf 9/Stunde, die nächtliche Sauerstoffsättigung auf minimal 70% mit Werten von 80–90% während 87% der Zeit. Die Entsättigungen dürften einerseits durch die vorbestehende chronische obstruktive Lungenerkrankung und andererseits durch eine Verteilungsstörung bei ausgeprägter Adipositas (BMI 37 kg/m^2) bedingt sein.
Diskussion: Aufgrund der Überproduktion von Wachstumshormonen kommt es zu einer Zunahme der Weichteile im Bereich des Rachens und zu einer Makroglossie. Nach erfolgreicher Therapie der Akromegalie sind solche Weichteilhypertrophien regredient, weshalb wir eine deutliche Besserung des obstruktiven Schlafapnoesyndroms dokumentieren konnten. Dies trug massgeblich zur Verbesserung des Allgemeinzustandes und der Lebensqualität der Patientin bei, indem die Tagesmüdigkeit deutlich reduziert werden konnte.

P76

Trimethoprim-induzierte cholestatische Hepatitis bei Compound-Heterozygotie für familiäre Haemochromatose

Pfister R., Jeker R., Reinhart W.H. (Chur)

Fallbeschreibung: Ein 62jähriger Patient wurde zugewiesen wegen eines subakuten, 2 Wochen nach Therapie mit Trimethoprim/Sulfamethoxazol aufgetretenen, schmerzlosen Ikterus. Die Laboruntersuchungen zeigten das Bild einer cholestatischen Hepatitis mit einer direkten Hyperbilirubinämie von 552 µmol/, einer 2-fach über der Norm erhöhten alkalischen Phosphatase und Transaminasen, welche im Verlauf auf das 4fache der Norm anstiegen. Eine virale oder autoimmune Hepatitis konnte ausgeschlossen werden, Coeruloplasmin und Alpha-1-Antitrypsin waren normal. Es bestand eine Hyperferritinämie (1207 µg//l) mit einer deutlich erhöhten Transferrinsättigung (82%), sodass eine mögliche Haemochromatose weiter abgeklärt wurde. Die Leberhistologie war mit einer Gallenabflusstörung vereinbar, es konnte eine Gallengangsschädigung und -proliferation sowie eine Siderose nachgewiesen werden. Aufgrund der ananmnestischen Angaben und der wiederholten unauffälligen sonografischen Befunden von Leber und Gallenwege war aber eine extrahepatische obstruktive Cholestase ausgeschlossen. Molekulargenetisch wies man eine sogenannte Compound-Heterozygotie nach, d. h. eine gleichzeitige heterozygote Mutation von C 282Y und H63D. Angesichts des zeitlichen Ablaufes und in Kenntnis der potentiell hepatotoxischen Wirkung von Trimethoprim gingen wir von einer

medikamentös induzierten Hepatitis aus. Die Erkrankung verlief protrahiert, wegen zunehmender psychomentaler Belastung aufgrund des anhaltenden therapierefraktären Pruritus musste der Patient während 3 Wochen hospitalisiert bleiben. Wir behandelten symptomatisch mit Cholestyramin und Naloxon. Die Cholestaseparameter waren erst im Verlaufe von 2 Monaten regredient (Gesamtbilirubin nach 2 Monaten 56 µmol/), die Hyperferritinämie persistierte aber unverändert hoch (2017 µg//l).
Diskussion: Bei diesem Patienten mit Trimethoprim-induzierter cholestatischer Hepatitis und Compound-Heterozygotie für familiäre Haemochromatose zeigte sich ein protrahierter Erkrankungsverlauf mit persistierend hohen Ferritinwerten auch nach Abklingen der Hepatitis. Bekannt ist, dass die Compound Heterozygotie eine Risikosituation für zusätzliche lebertoxische Situationen ist und somit ein Zusammenhang zwischen einem protrahiertem Verlauf einer medikamentösen Hepatitis und der Heterozygotie postuliert werden kann, obwohl es in der Literatur keine solchen Fallbeschreibungen gibt.

P77

Physicians' ability to estimate patient's compliance with antihypertensive medication in primary care: pilot study

Martina B., Battegay E., Tschudi P. (Basel, Basel und Zürich)

Background: The ability of primary care physicians to estimate patients' compliance with cardiovascular medication is barley investigated.
Objective: To determine physicians' accuracy to predict their patients' compliance with antihypertensive therapy.
Methods: In a prospective observational study patients with the clinical diagnosis of hypertension were recruited by general practitioners or by hospital-based physicians from a Medical Outpatient Department. Doctors were asked to give an unaided estimation of the compliance with medication of their patients by using a visual analogue scale (VAS). Compliance was monitored by using a medical event monitoring system (MEMS 6, AARDEX Ltd, Zug, Switzerland). Patients were asked to self-estimate the accuracy of medication taking on a VAS on the day of recruitment. Outcome measures were MEMS monitored compliance and estimated compliance using a VAS consisting of a horizontal line, which was 100 mm in length.
Results: Three general practitioners and six hospital-based physicians took part and estimated medication taking of 42 of their patients. Patients were monitored by MEMS on 42 days (±14) on average. Nine out of ten subjects were on a once daily regimen and 85% of participants have taken their medication for more than one year. Mean MEMS measured compliance for timing compliance (± SD, range), correct dosing, and taking compliance was 82% (±27, 0–100%), 87% (±24, 4–100%), and 94% (±18, 4–108%), respectively.Physicians' estimation of their patients' compliance was 92% (±15) on average. Spearman rank correlation coefficient for the association between physician's estimation and MEMS measured timing compliance, correct dosing, and taking compliance was 0.42 ($p = 0.006$), 0.47 ($p = 0.002$), and –0.02 ($p = 0.888$), respectively. Patients self-estimated their accuracy of medication taking at a value of 98% (±2, range 83 to 100%). Spearman coefficients were 0.27 ($p = 0.08$) for timing compliance, 0.25 ($p = 0.12$) for correct dosing, and 0.11 ($p = 0.51$) for taking compliance.
Conclusion: Physicians' estimation of their patients' compliance with antihypertensive medication showed a low to modest, but significant correlation to MEMS measured compliance. Data suggest that physicians tend to overestimate the accuracy of patients' medication taking. However, physicians' judgment of medication taking seems to be more accurate than patients' self-estimation.

P78

Advice and counselling to stop smoking in patients admitted on a general internal medicine ward

Miedinger D., Nester N., Schafroth S., Tamm M., Stolz D., von Garnier C., Leuppi J.D. (Basel, Bern)

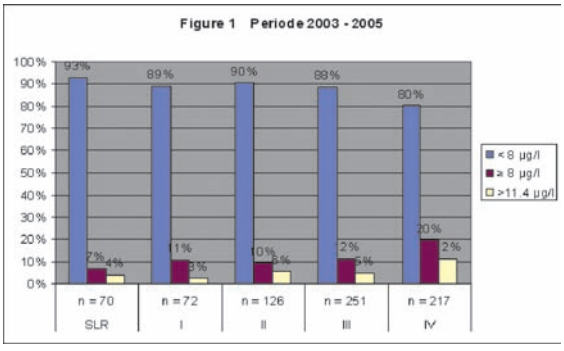
Introduction: Smoking is a major harm to health. Being hospitalized may trigger attemps to stop smoking.
Aims: To determine smoking behaviour, willingness to quit smoking and to participate in a smoking cessation program. To determine if patients were told to stop smoking and offered help to quit smoking by doctors before the current hospitalization.
Methods: Interviewer administered questionnaire. Subjects: Patients hospitalized on a general internal medicine ward from beginning of September 2006 until middle of October 2006 at the University Hospital in Basel, Switzerland.
Results: 338 patients were admitted an a general internal medical ward during the study period. In 289 (86%) the questionnaire could be completed. 58 (20%) of 289 patients were smoking in the last seven days before admission, 124 (43%) were never-smokers and 107 (37%) were former smokers. Current smokers mean age was 53 years (range 19–85 years), 41 (71%) were male. The mean Fagerstroem of nicotine dependency score was 4,2 (SD 2,6). 34 (59%) were willing to stop smoking and 26 (45%) were willing to participate in a smoking cessation program. Before hospitalisation, 29 (50%) have been told to stop smoking and 17 (29%) have been offered help to stop smoking by a doctor.
Conclusion: Every second smoker on a general internal medicine ward would like to stop smoking. Only half of them have been told to stop smoking before by a doctor and only a third have actually been offered help in doing so. Hospital-based smoking cessation intervention might be provided systematically to all smokers admitted on a general internal medicine ward.

P79

Schweregrad der Hymenopterengiftallergie in Bezug zum basalen Serumtryptase-Wert

Meier R., Haeberli G., Müller U.R., Helbling A. (Bern)

Einleitung: Die Assoziation zwischen erhöhter basaler Serumtryptase (bsT) und dem Schweregrrad einer allergischen Allgemeinreaktion nach einem Bienen- oder Wespenstich ist gut etabliert. Eine bsT Konzentration >11,4 ng/ml (95-Perzentile) gilt als erhöht. Gemäss einer kürzlich publizierten Leitlinie (Allergo J 2004;13:440–2) können allerdings schon bsT zwischen 8 und 10 ng/ml ein erhöhtes Risiko für eine Systemreaktion nach einem Hymenopterenstich bedeuten. In dieser Untersuchung wollen wir die Verteilung der bsT bezogen auf den Schweregrad einer allergischen Reaktion – inklusive schwere Lokalreaktion – bei Hymenopterengift-allergischen Patienten analysieren.
Methode: 736 Patienten mit einer gesicherten Hymenopterengiftallergie und vorhandener bsT aus den Jahren 2003 bis 2005 sind eingeschlossen. Die bsT wurde mittels UniCAP Tryptase Fluoroenzyme Immunoassay bestimmt (Pharmacia Diagnostic, Uppsala, Sweden). Basierend auf dem sbT wurden die Patienten folgenden Gruppen zugeteilt: 639 Pat. (86,8%) hatten eine bsT <8,0 ng/ml (durchschnittlich 4,2 ng/l), 48 Pat. (6,5%) eine bsT zwischen 8 und 11,4 ng/ml (durchschnittlich 9,6 ng/l) und 49 Pat. (6,6%) eine bsT >11,4 ng/ml (durchschnittlich 16,8 ng/ml; range 12,0–33,9 ng/ml).
Ergebnisse: Die Verteilung der bsT in Bezug zum Schweregrad der allergischen Reaktion (nach H.L. Mueller) ist in Figur 1 aufgeführt.
Konklusion: Eine Erhöhung der bsT findet sich primär bei Patienten mit einer schweren Allgemeinreaktion nach einem Hymenopterenstich. Interessant ist aber, dass die Inzidenz einer erhöhten bsT bei Schweregrad III und jenen mit einem Schweregrad I/II ähnlich ist. Bemerkenswert ist ferner, dass eine Korrelation nicht nur bei Patienten mit bsT-Werten >11,4 ng/ml, sondern auch bei jenen mit bsT-Werten ≥8,0 ng/ml beobachtet werden konnte. Diese Daten zeigen, dass einer bsT-Konzentration ≥8,0 ng/ml bereits eine Bedeutung hinsichtlich Auftreten einer Systemreaktion nach einem Hymenopterenstich zukommen kann.
Abbildung 1



P80

Medical and pharmacological direct costs over 12 weeks of stopping cigarette smoking

Digon P., Cornuz J., Wasserfallen J-B. (Lausanne)

Introduction: Stopping smoking is difficult, associated with numerous relapses despite pharmacological nicotin replacement therapy (NRT), and costs of quitting are not well known.
Patients and Methods: The 481 patients involved in a program to stop smoking were followed-up for 12 weeks. Personal characteristics, number of outpatient visits, dosage and frequency of use of NRT as well as date of relapse were prospectively collected. Unit costs of visits and NRT were identified from official tariffs, and individual cost of care until relapse or program end as well as cost per week of follow-up were computed. Comparisons were carried out between the groups of patient finishing or leaving prematurely the program, as well as between the groups with or without relapse at the end of the program.
Results: Of the 209 men and 272 women included, 347 patients (72%) finished the program. Among them, 240 patients (70%) succeeded in quitting, and 107 patients (30%) relapsed. As compared with the group leaving prematurely the program (134 patients), the group with complete follow-up (347 patients) was older (mean age 43.7 ± 9.6 years vs 40.8 ± 9.9 years, p = 0.003), the percentage of patients living in couple higher (64% vs 47%, p = 0.001), and the number of attempts to quit during the previous year lower (26% vs 36%, p = 0.033). Mean weekly costs of visits were lower (CHF 80.3 ± 6.7 vs 86.8 ± 12.2, p <0.001), mean weekly costs of NRT higher (CHF 24.6 ± 13.7 vs 17.2 ± 14.3, p <0.001), so that mean total costs per week were similar (CHF 104.9 ± 16.7 vs 104.0 ± 15.4, p = 899). As compared with the group relapsing at the end of the program (107 patients), the group succeeding in quitting (240 patients) was more often living in couple (68% vs 55%, p = 0.029). Their mean weekly costs of visits were higher (CHF 81.2 ± 6.1 vs 78.4 ± 7.6, p = 0.001), while their mean weekly costs for NRT were similar (CHF 24.2 ± 12.6 vs 25.4 ± 15.9, p = 0.711). Mean total costs per week were similar (CHF 105.4 ± 15.4 vs 103.8 ± 19.4, p = 0.252). More intensive NRT at week 4 increased the probability not to relapse at the end of the program.
Conclusions: Over 12 weeks, medical and pharmacological costs of stopping smoking are low. Good medical and social support as well as adequate NRT seem to play a role in successful quitting.

P81

Lymphom der Prostata – Diagnose auf den «2. Stich»

Vetsch G., Baumann C., Kläy M., Leupin N., Rentsch C., Müller-Garamvölgyi E., Bürgi U., Schiemann U. (Bern)

Hintergrund: Maligne Lymphome der Prostata sind eine klinische Rarität. In der Literatur werden insgesamt nur etwa 165 Fälle beschrieben, in denen ein primäres Lymphom oder eine sekundäre Infiltration der Prostata durch ein Lymphom vorlag.
Fallbeschreibung: Berichtet wird der Fall eines 59jährigen Patienten mit einer unscharf begrenzten Raumforderung im Bereich der Prostata bei normalem PSA, einer Wirbelkörperfraktur und bilateralen Nebennierenvergrösserungen. Eine zweizeitige Prostatastanzbiopsie erbrachte den Befund eines diffusen grosszelligen B-Zell-Non-Hodgkin-Lymphoms. Weitere Staging-Untersuchungen ergaben Anhaltspunkte für das Vorliegen eines epiduralen Befalls. Es wurde eine Polychemotherapie inklusive intrathekaler Applikation initiiert, unter der sich die Lymphommanifestationen bei einem ersten Zwischenstaging nach 4 Zyklen deutlich zurückgebildet hatten.
Schlussfolgerung: Bei einer Raumforderung im Bereich der Prostata muss neben einem Prostatacarcinom als weitaus häufigste Tumorentität, auch an ein primäres Lymphom oder eine sekundäre Lymphominfiltration der Prostata gedacht werden, insbesondere bei einem normalen PSA.

P82

Szintigrafischer Nachweis von multiplen peripheren Lungenembolien bei pulmonal arterieller Hypertonie und unauffälliger Angio-Computertomografie

Bochsler S.C., Wertli M., Ballmer B.E. (Winterthur)

Fallpräsentation: Bei einer 75jährige Patientin mit schwerem Parkinson Syndrom wurden im Rahmen der Abklärungen nach akutem cerebrovaskulärem Ereignis (CVI) mit sensomotorischem Hemisyndrom rechts, Aphasie und Neglect, rezidivierende periphere arterielle Hypoxämien festgestellt. Die Ursache dafür war echokardiografisch eine schwere pulmonal arterielle Hypertonie (PAH) mit einem RV/RA-Gradienten von 77 mm Hg. Die arterielle Blutgase zeigte eine respiratorische Partialinsuffizienz (pO_2 6,5 kPa, pCO_2 4,5 kPa, pH und BE normal) und es bestand eine Polyglobulie (Hämoglobin 17,5 g/dl, Hämatokrit 58%). Die weitere Ursachenabklärung des Insults schloss eine Carotisstenose oder eine Rhythmusstörung aus. Die nächtliche Oxymetrie bestätigte die Hypoxämien (wach leichte, nachts mittelschwere), Hinweise auf ein Schlafapnoesyndrom oder eine Cheyne-Stokes-Atmung lagen nicht vor. Eine Lungenfunktionsprüfung zeigte keine grobe Pathologie und eine Schilddrüsenfunktionsstörung konnte ausgeschlossen werden. Computertomografisch fanden sich keine Lungenembolien und keine interstitielle Pneumopathie als Ursache der PAH. Die ergänzend durchgeführte Lungenperfusionsszintigraphie mit 99m-Tc zeigte multiple bilaterale Defektzonen in beiden Lungen, mit multiplen peripheren Lungenembolien vereinbar.
Diagnose: Chronische thromboembolische pulmonale Hypertonie (CTEPH).
Diskussion: Als Ursache für eine periphere Hypoxämie fand sich im Rahmen einer Abklärung bei CVI echokardiographisch eine schwere PAH. Da die CTEPH eine potentiell heilbare Erkrankung ist, sollte sie in jedem Fall gesucht werden. Auch neuere Untersuchungen zeigen, dass die Szintigrafie zum Nachweis peripherer Lungenembolien der Computertomografie überlegen ist. Unser Fall zeigt eindrücklich, wie die Szintigrafie trotz unauffälliger Computertomographie multiple Defekte, entsprechend multiplen peripheren Lungenembolien, nachweisen konnte. Bei Patienten mit Parkinson Syndrom sollte an rezidivierende thromboembolische Ereignisse gedacht werden. Sie zählen neben den Pneumonien zu den zweithäufigsten Todesursachen.

P83

Kryptokokken-Meningoenzephalitis bei nicht-immunsupprimiertem Patienten

Hodel Th., Müller M., Rossi M., Stellmes P., Briner V. (Luzern)

Fallbericht: Ein 1968 geborener Mann wurde im Herbst 2007 wegen Erbrechen und Agitiertheit hospitalisiert. Zuvor hatte er bereits seit sechs Monaten intermittierend unter Übelkeit, Kopfschmerzen und Verwirrtheit gelitten. Bei Spitaleintritt bestanden frontale Kopf- und ziehende Nackenschmerzen ohne Meningismus. Psychopathologisch fiel ein pseudoneurasthenes Syndrom auf. Die neurologischen Befunde, der internistische Status und die Laboruntersuchungen inklusive Entzündungsparameter fielen normal aus. Bei normalem Druck wies der l Zellen (normalμLiquor 170/ <4), vorwiegend polynukleär, einen Gesamteiweisswert von 2,99 g/l (normal <0,45) und eine Glucosekonzentration von 1,1 mmol/l auf. Die mikrobiologischen und serologischen Liquoruntersuchungen fielen negativ aus. Das EEG zeigte diskrete frontotemporale Verlangsamungsherde. Im MRI nahmen die perimesencephalen Leptomeningen Kontrastmittel auf. Unter Steroidmedikation mit 100 mg Prednisolon täglich liessen die Beschwerden des Patienten vorübergehend nach. Zwei Wochen später erfolgte eine erneute Hospitalisation mit Meningismus und Hirndruckzeichen. Bei erhöhtem Liquordruck über 55 cmH_2O liess sich nun im Liquor kulturell Cryptococcus neoformans als Ursache für die chronisch verlaufende Meningoenzephalitis nachweisen. Hinweise für eine Immunsuppression bestanden nicht. Wir behandelten während zehn Tagen mit Amphotericin B und anschliessend wegen einer erhöhten Hemmkonzentration für Fluconazol mit Voriconazol oral unter ausschleichender Steroidmedikation mit Dexamethason bei regredienten Druck- und Entzündungswerten des Liquors.
Diskussion: Kryptokokken sind bekapselte Sprosspilze, die weltweit vor allem in Vogelkot vorkommen. Die Infektion beim Menschen erfolgt aerogen. Die Erreger weisen eine ausgesprochene Affinität für das zentrale Nervensystem auf. Nicht-immunsupprimierte Patienten leiden oft während Wochen bis Monaten unter unspezifischen Sym-

ptomen bis zur Diagnosestellung, welche direkt mittels Tuschepräparat oder Antigennachweis im Liquor erfolgt.
Schlussfolgerung: Eine Kryptokokken-Infektion ist in der Differentialdiagnose subakut oder chronisch verlaufender Meningoenzephaliti-den selbst bei immunkompetenten Patienten zu berücksichtigen. Die medikamentöse Behandlung erfolgt mit Amphotericin B, bei schwerem Verlauf kombiniert mit Flucytosin, bis die Liquorkulturen negativ werden. Anschliessend ist eine orale Therapie mit einem Triazol-Antimykotikum während drei bis sechs Monaten fortzusetzen.

P84

Impact d'un schéma de mobilisation précoce après infarctus myocardique aigu sur la durée de séjour et l'utilisation des ressources

Moret C., Simard N., Waeber G., Lamy O. (Lausanne)

Contexte: Malgré les récentes avancées dans la prise en charge de l'infarctus myocardique aigu – angioplastie primaire, les recommandations internationales – la durée moyenne de séjour (DMS) des patients hospitalisés a peu évolué en Suisse. Elle se situe entre 9 et 11 jours.
Objectif: Evaluer l'impact sur la DMS et la faisabilité d'un schéma de monitoring simplifié et de mobilisation précoce appliqué aux patients avec infarctus myocardique aigu à faible risque de complications (IMFRC): âge <76 ans, maladie coronarienne mono- ou bi-tronculaire complètement revascularisée, sans symptômes d'insuffisance cardiaque ni troubles du rythme.
Méthodes: Etude prospective observationnelle incluant les patients avec IMFRC admis au CHUV. Les patients transférés des ou vers les hôpitaux périphériques ont été exclus. Ces résultats ont été comparés à la prise en charge effectuée en 2005. Le devenir des patients 3 mois après la sortie de l'hôpital est analysé.
Résultats: De janvier à décembre 2007, 105 patients avec IMFRC ont été admis au CHUV dont 68 transférés en périphérie ont été exclus. Les 7 femmes et 30 hommes avaient un âge moyen de 57 ± 11 ans. La DMS était de 6,6 ± 3,4 jours avec une médiane de 5 jours. La répartition du séjour était en moyenne: 1,3 ± 0,7 jours aux soins intensifs; 0,8±1,1 jours aux soins continus et 4,3 ± 2,6 en division générale. Par rapport à l'année 2005 où les 55 patients inclus avaient les mêmes caractéristiques, la DMS était significativement plus longue: 8,0 ± 4,0 jours (p <0,05) avec une médiane de 7 jours. Les séjours en 2005 se répartissaient en: 1,8 ± 0,8 jours aux soins intensifs (p = 0,05); 1,5±1,8 jours aux soins continus (p <0,05) et 4,8 ± 3,5 jours (p >0,05) en division générale. Il n'y a pas eu de différence dans la survenue de complications hospitalières entre 2005 et 2007. L'économie réalisée en 2007 est d'environ 4000 francs par patient, soit une diminution des coûts par patient de 25% par rapport à l'année 2005.
Conclusions: Malgré les difficultés d'introduction du schéma, un monitoring simplifié et une mobilisation précoce post-infarctus ont pu être appliqués à la majorité des patients avec IMFRC. Il a permis non seulement de diminuer la DMS mais surtout de mieux utiliser les ressources, notamment en diminuant la durée d'occupation des lits de soins intensifs et de soins continus, et ceci sans augmenter le risque de complications.

P85

Nicht jede gastroösophageale Varize bedeutet das Vorliegen einer Leberzirrhose. Eine ungewöhnliche Differentialdiagnose einer massiven oberen GIT-Blutung

Weder C., Jochum W., Schneemann M. (Zürich)

Ein aus Syrien stammender 25jähriger Asylbewerber wurde wegen endoskopisch unstillbarer oberer Gastrointestinalblutung bei Ösophagusvarizen zugewiesen. Trotz endoskopischer Varizenligierung und Einlage einer Sengstaken-Sonde persistierte die Blutung. Es musste ein transjugulärer intrahepatischer portosystemischer Stent (TIPS) eingelegt werden. Dabei wurde ein auf 55 mm Hg erhöhter Pfortaderdruck gemessen (Norm: 2–6 mm Hg). Klinisch ergab sich kein Hinweis auf eine Ursache der portalen Hypertonie (Alkoholabusus, Hepatitis B/C, Schistosomiasis, Budd-Chiari-Syndrom). Histologisch wurde in der Leberbiopsie weder eine Zirrhose noch eine chronische Lebererkrankung nachgewiesen, so dass die Diagnose einer idiopathischen portalen Hypertonie gestellt wurde. Die idiopathische portale Hypertonie zeichnet sich durch einen erhöhten Druck im Portalkreislauf ohne Vorliegen einer Leberzirrhose aus. Verschiedene Faktoren wurden mit der Entwicklung dieser Erkrankung in Verbindung gebracht: Infektionen, Arsen-Vergiftung, Autoimmunerkrankungen. Man nimmt an, dass diese Faktoren bei genetisch prädisponierten Personen zu Mikroembolien in kleinen Portalvenenästen führen. Histologisch gibt es keine pathognomonischen Veränderungen; folgende Befunde wurden jedoch beschrieben: Portalfibrose, Intimafibrose in mittleren und kleinen intrahepatischen Portalvenenästen mit Obliteration des Lumens, Dilatation der Sinusoide und noduläre Hyperplasie der Hepatozyten. Klinisch präsentieren sich die Patienten mit oberer Gastrointestinalblutung bei Varizen, Splenomegalie, Hypersplenismus (Zytopenien) und erhaltener Leberfunktion. Aszites, Ikterus oder eine hepatische Enzephalopathie entwickeln sich selten. Die Behandlung richtet sich nach den vorliegenden Komplikationen. Bei Varizen ist eine Primärprophylaxe mit Beta-Blocker / endoskopischer Sanierung und nach Blutung eine Sekundärprophylaxe mit endoskopischer Sanierung der Varizen indiziert. Nicht stillbare Blutungen und eine symptomatische Hypersplenie sollten chirurgisch, oder wie in unserem Fall, mit Einlage eines TIPS angegangen werden. Im Gegensatz zu Indien und Japan wird die Diagnose einer idiopathischen portalen Hypertonie in Europa nur selten gestellt. Unsere Fallbeschreibung zeigt jedoch, dass diese Differentialdiagnose bei Patienten mit oberer Gastrointestinalblutung bei Varizen auch in der Schweiz in Betracht gezogen werden muss.

P86

Klinik-externe und -interne Determinanten der Spitalaufenthaltsdauer

Prof. Ballmer P.E. (Winterthur)

Fragestellung: Im Zusammenhang mit der bevorstehenden Einführung der APDRG (All Patient Diagnosis Related Groups), ist es Ziel dieser Studie, Faktoren, welche die Spitalaufenthaltsdauer (LOS; length of hospital stay) von Patienten an einer allgemein-internistischen Klinik beeinflussen, zu erfassen. Damit soll Einsicht gewonnen werden, wie die LOS ohne Beeinträchtigung der Behandlungsqualität vermindert werden kann.
Methodik: Die LOS wurde entsprechend der NCHS (National Center for Health Statistics) definiert als: 1.Quotient der gesamten Anzahl Hospitalisationstage einer Patientengruppe zur gesamten Anzahl Entlassungen und 2. Quotient der gesamten Anzahl Pflegetage einer Patientengruppe zur gesamten Anzahl Entlassungen. Bei der ersten Gleichung wird die gesamte Hospitalisationsdauer mittels Ein- und Austrittsdatum erfasst. Bei der zweiten Gleichung wird das Eintrittsjedoch nicht das Austrittsdatum berücksichtigt. Anstelle des Austrittsdatums wird hier das Ende der benötigten Pflegetage erfasst, was dem medizinisch frühest möglichen Entlassungsdatum entspricht. Bei allen Patienten zweier internistischer Stationen wurden während 2 Monaten die Zeitintervalle vom Eintritt bis Diagnosestellung (T-1), Therapiebeginn (T-2), frühest möglichen Entlassungstag (T-3) und wirklichem Entlassungstag (T-4) prospektiv untersucht.
Resultate: Wir präsentieren präliminäre Resultate der ersten 26 Patienten. Von diesen Patienten wiesen lediglich 10 eine LOS ohne Verzögerungen (38,5%) auf, während es bei 16 zu Verzögerungen (61,5%) kam. Die LOS aller Patienten betrug 230 Tagen, wovon 77 Tage (33,5%) durch Verzögerungen verursacht wurden. Untersuchungen (total 75) führten in 8 Fällen (10,7%) zu einer Verzögerung (Klinik-intern), während post-stationäre Massnahmen (total 8) in 5 Fällen (62,5%), durch Wartezeiten auf Verlegungen (Klinik-extern) in Pflegeheime, Rehabilitationen u.a.m., die LOS verlängerten. Weitere Verzögerungen ergaben sich durch Wochenenden in denen der diagnostische oder therapeutische Prozess still stand (29,0%), durch Komplikationen, palliative Situationen sowie durch andere Klinikexterne Faktoren.
Schlussfolgerung: Unsere Interimsanalyse zeigt, dass sich Verzögerungstage gleichmässig auf Klinik-interne (46,8%) und Klinikexterne Ursachen (53,2%) verteilen. Klinik-interne Verzögerungsfaktoren lassen sich durch Optimierung des Patientenprozesses beeinflussen, während die Klinik-externen Faktoren (z.B. Warten auf einen Pflegeplatz) kaum von uns beeinflusst werden können.

P87

Zeuge Jehovas lehnt vital indizierte Bluttransfusion ab – Was ist zu tun? Entwicklung einer transparenten Behandlungsleitlinie

Roggo A., Kramer D., Seidl Ch. (Bern, Würzburg [D], Visp)

Fragestellung: Im Rahmen einer in dieser Dimension erstmals erstellten Feldstudie wurde die reelle forensische Erfahrung im Zusammenhang mit zwar *vital indizierter*, jedoch *abgelehnter Bluttransfusion* bei Angehörigen der Zeugen Jehovas erhoben, um daraus mögliche Vorgehensweisen für die Praxis abzuleiten.
Methode: Zur Evaluation eines Beobachtungs-Zeitraums von 20 Jahren (1986–2005) wurden 529 standardisierte Fragebogen versandt. Befragt wurden schweizweit alle Akutspitäler, kantonalen Gerichte erster und zweiter Instanz und das Bundesgericht; zudem die kantonalen Vormundschaftsbehören, Sanitätsdirektoren und Kantonsärzte. Ergänzend wurden Interessengruppen der medizinischen Fachgesellschaften und Haftpflichtversicherer im Gesundheitswesen einbezogen.
Resultat: Total 382 Fragebogen wurden zurückgesandt, somit eine überdurchschnittlich hohe Quote von 72%. Insgesamt wurden nur 6 Ereignisse festgehalten: Eine Meldung von einem Kantonsarzt; 5 aus Akutspitälern (in einer Situation mit Todsfolge wurde diese als Offizialdelikt strafrechtlich anhängig gemacht, das Verfahren beim Untersuchungsrichter eingestellt). Keines der antwortenden 205 Gerichte hatte jemals über einen entsprechenden Streitfall zu entscheiden. Bei Haftpflichtversicherungen bzw. Standesorganisationen gingen keine Meldungen ein.
Erkenntnis und Schlussfolgerung: Wir können davon ausgehen, dass nur eine Minderheit der Bevölkerung im Ernstfall eine Bluttransfusion ablehnen würde, aus welchen Gründen auch immer. Dennoch ist die inhaltliche Brisanz für Ärzte im Einzelfall hoch, da ein Entscheid erwartet wird. Diese sind einer beinahe unlösbaren, paradoxen juristischen Pflichtenkollision (handeln zur Lebensrettung / unterlassen in Achtung des Selbstbestimmungsrechts?) und damit einem Spannungsfeld zwischen «juristischem Recht» und dem geleisteten «hippokratischen Eid» ausgesetzt. Oft entsteht gerade aus dieser Pflichtenkollision und einer verbreiten Grauzone bezüglich Rechtssicherheit ein Gewissensnotstand, der den meisten Ärzten hinlänglich bekannt ist. Die Abteilung für Medizinrecht / Institut für Rechtsmedizin Universität Bern trägt den in der Feldstudie erhobenen Resultaten und der allgemeinen Problematik Rechnung. An hand eines strukturierten Lösungsweges werden entsprechend Algorithmen vorgestellt: Vital indizierte Bluttransfusion Ja / Nein bei einem Urteilsfähigen / Nichturteilsfähigen in einer Elektiv- / Notfall-Situation.

P88

Behandlungsleitlinien im Falle der Verweigerung einer vital indizierten Bluttransfusion in der Elektiv- / Notfallsituation beim Urteilsfähigen/Nichturteilsfähigen

Roggo A., Kramer D., Seidl Ch. (Bern, Würzburg [D], Visp)

Die Behandlungsleitlinien bei Verweigerung einer vital indizierten Bluttransfusion für die Elektivsituation bzw. Notfallsituation beim Urteilsfähigen / Nichturteilsfägigen werden in Form zweier so genannter «Decision Tree Algorithms» in Ergänzung zum Referat: *Zeuge Jehovas lehnt vital indizierte Bluttransfusion ab – Was ist zu tun? Entwicklung einer transparenten Behandlungsleitlinie* vorgestellt und zur praktischen Umsetzung im klinischen Alltag empfohlen bzw. persönliche Erfahrungen der Kongressteilnehmer eingeholt.

P89

Seltene Manifestation einer Lymphomerkrankung

Maile S., Semadeni G.M., Imoberdorf R., Dommann-Scherrer C., Müller A. (Winterthur)

Fall: Eine 66jährige Patientin klagte 6 Monate über anhaltende Müdigkeit und Zustandsverschlechterung. Im Labor fanden sich erhöhte Entzündungsparameter, in umfassenden Abklärungen konnte keine Ursache für die Beschwerden gefunden werden. Plötzlich trat ein febriler Zustand sowie ein teleangiektatisches Erythem und Ödem am Stamm, an den Mammae und Oberschenkeln auf. Unter dreiwöchiger Therapie mit verschiedenen Antibiotika erfolgte keine Besserung, das CRP blieb hoch. Beim stationären Eintritt zeigten sich am Hals links und infraclaviculär vereinzelte vergrösserte Lymphknoten.
Diagnose: Es wurden Hautbiopsien sowie ein vergrösserter Lymphknoten (Hals) entnommen. In der Haut morphologisch Nachweis von intravasalen blastären Zellen, immunhistochemisch CD20+, CD5+, bcl-6+, 100%Ki-67+: Infiltration eines ausschliesslich intravasalen grosszelligen B-Zell-Lymphoms. Im Lymphknoten ausgedehnte Infiltration durch ein diffuses grosszelliges Lymphom der B-Zellen, CD20+, CD5+, bcl-6+, 90%Ki-67+. Als Nebendiagnosen Prolaktinerhöhung (Mikroadenom Hypophyse), hypophysäre Hypothyreose und Nebennierenrindeninsuffizienz. Im CT keine weiteren Lymphknotenvergrösserungen, im Liquor, MRI Schädel und Knochenmark kein Hinweis auf Lymphominfiltration.
Verlauf: Eine Polychemotherapie mit Zusatz des CD20-Antikörpers Rituximab (R-CHOP) führte zu einer vollständigen Remission. Ebenso wurde eine intrathekale Prophylaxe mit Ara-C durchgeführt. Zur Prolaktinsenkung wurde Cabergolin verabreicht, Thyroxin bei Hypothyreose. Innerhalb von 3 Wochen wurden 20 kg Hautödem ausgeschwemmt, das Erythem ist verschwunden, die Müdigkeit ist regredient.
Diskussion: Das intravaskuläre Lymphom (IVL) ist durch eine intravaskuläre Proliferation von Lymphomzellen charakterisiert, welche auf einen besonderen Homing-Mechanismus hinweist. In diesem Fall wurde konkomitierend eine klonale Vergesellschaftung mit einer soliden Lymphomkomponente im Lymphknoten zervikal festgestellt. Häufigste Manifestationen der Erkrankung sind unspezifische Entzündungszeichen. Prädominant weist das IVL einen kutanen und zerebralen Befall auf, das periphere Blut ist selten betroffen. Bei Diagnosestellung ist das IVL eine disseminierte Erkrankung, bei dieser Patientin liegt ein Stadium IVB vor. Nach Polychemotherapie haben rein kutane Varianten eine bessere Prognose. Rezidive sind nach kompletter Remission häufig. Ein Drittel dieser betreffen das zentrale Nervensystem, weshalb eine intrathekale Prophylaxe indiziert ist.

P90

Paraneoplastische cerebelläre Degeneration (anti-Yo-positiv) – eine ungewöhnliche Primärmanifestation eines Tubenkarzinoms

Schmid S., Stillhard G., Grabherr R., Federspiel B. (Horgen, Wädenswil)

Fall: Eine 51jährige Frau wurde wegen seit 2 Wochen progredientem Schwankschwindel und Gangunsicherheit zugewiesen. Neurologisch fiel eine Dysarthrie, undulierende Diplopie und eine generalisierte Schwäche aller Extremitäten bei normaler motorischer Nervenleitgeschwindigkeit des N. peroneus und N. medianus beidseits auf. Das Schädel MRI war unauffällig. Im Liquor fand sich eine leichte Pleozytose mit Eiweisserhöhung. Die Borrelien-Serologie, inkl. intrathekale AK und die Herpes-PCR im Liquor waren negativ, ebenso die Serologien auf CMV, EBV, HIV und Mycoplasmen. Innert zwei Wochen rasche Krankheitsprogression mit Steh- und Gangunfähigkeit, deshalb Bestimmung von onkoneuronalen Antikörpern. Es konnten anti-Yo-AK nachgewiesen werden. Zusammen mit einem eindrücklichen cerebellären blickmotorischen Syndrom mit intermittierend vertikalen Doppelbildern, Dysarthrie, progredienter Stand-/Gang- und Rumpfataxie konnte die Diagnose einer anti-Yo-positiven paraneoplastischen cerebellären Degeneration (PCD) gestellt werden. Die folgende Tumorsuche mit Mammographie, CT Thorax und Abdomen, Gastro- und Koloskopie, Bronchoskopie und Zystoskopie blieb ohne Hinweis für eine Neoplasie. In einer diagnostischen Laparaskopie präsentierte sich ein 2,3x1,5x1,2 cm kleiner Tumor im Bereich der linken Tube, der histologisch einem wenig differenzierten serösen Adenocarcinom entsprach.
Diskussion: Die cerebelläre Degeneration gehört zu den klassischen paraneoplastischen neurologischen Syndromen (PNS). Für die Diagnosestellung gelten folgende Kriterien: Entwicklung eines schweren pancerebellären Syndroms in weniger als 12 Wochen ohne kernspintomographisch sichtbare cerebelläre Atrophie. Erstes Symptom ist häufig eine zunehmende Gangataxie. Typischerweise findet sich in der Frühphase der Erkrankung nur eine unspezifische Pleozytose im Liquor. In unserem Fall fanden sich anti-Yo-AK, welche in über 98% der Fälle mit einem Mamma-, Ovarial- oder Endometriumkarzinom, selten Adenocardinom assoziiert sind und deshalb eine aggressive

Tumorsuche verlangen. Da die natürliche Immunantwort gegen den Tumor oft biologisch effektiv ist, können die Tumore für lange Zeit klein und klinisch inapparent bleiben, was die Suche wie in unserem Fall zu einer grossen Herausforderung macht. Leider ist das klinische Ansprechen auf eine Antitumortherapie und/oder Immunsuppression bei der anti-Yo-positiven PCD nur wenig erfolgsversprechend.

P91

Critical incidence reporting System (CIRS): Erfahrungen in der Einführungsphase einer medizinischen Klinik

Rochat Ph., Frauchiger B. (Frauenfeld)

Die Erfassung von kritischen Ereignissen (Critical Incidents, CI) mit potentiellem Schaden für die Patienten wird zur Reduktion von Systemfehlern im Qualitätsmanagement von Spitälern eingesetzt. Wir berichten über unsere bisherigen Erfahrungen.
Methodik: Einführung in unserer 80-Betten-Klinik im April 05 mittels Papierformular (obligate Angabe nur Beschreibung des CI). Im Januar 2007 Wechsel auf spitalweit eingesetzte, anonyme Informatiklösung. Analyse der Meldefrequenz, der CI und der daraus getroffenen Massnahmen. Quartalsweise klinikinterne Konferenzen (Pflege, Ärzte) mit Fokussierung auf Lösungsansätze.
Resultate: Nach wenigen Tagen trafen die ersten Meldungen ein, bei Papierversion immer mit Personalien (Patient + Meldende). Die Meldefrequenz stieg von 1,1/Wo (2005) auf 1,3/Wo (2006) und nach Wechsel auf Informatikprogramm auf 2,9/Wo. Die Pflege (65%, 60%, 82%)* meldete häufiger als die Ärzte (31%, 34%, 17%)* und war auch häufiger Ursprung (56%, 54%, 74%)* der CI. Die häufigsten CI umfassten falsche Medikamentendosis (28%, 36%, 34%)*, Patientenverwechslungen (16%, 18%, 9%)*, Beschriftungsfehler (14%, 4%, 2%)*, Dokumentationsfehler (12%, 10%, 25%)*, Medikamentenverwechslungen (5%, 10%, 4%)*. (7%, 24%, 12%)* der CI betrafen Antikoagulantien, insb. Heparin (Infusomatenproblem). 2007 wurden 13 falsche Insulinapplikationen erfasst. Als häufigste Ursachen wurden verminderte Aufmerksamkeit (49%, 58%, 33%)*, Arbeitsstress (23%, 22%, 12%)* und Kommunikationsprobleme (25%, 20%, 19%)* genannt. «Wissen/situative Aufmerksamkeit» waren der Hauptgrund zur Verhinderung einer Komplikation (31%, 42%, 50%)*. Die CI wurden meist als «vermeidbar» beurteilt (75%, 92%, 92%)*. 5 technische und 11 organisatorische Massnahmen wurden umgesetzt.
Schlussfolgerungen: 1) Konstruktiver und offener Umgang mit CI führte von Anfang an zu einer breiten Akzeptanz mit gutem Meldeverhalten. 2) Die Meldefrequenz stieg mit Einführung der Informatiklösung (Anonymität, leichterer Zugang?, DD: zunehmender Arbeitsanfall). 3) Was häufig gemacht wird, wird auch häufig falsch gemacht. 4) Bekannte Fehler werden eher wieder gemeldet. 5)Weniger Kontrollmechanismen, mehr vielschrittige Handlungen und besseres Meldeverhalten bei Pflege führen zu dort mehr erfassten CI. 6) Aus den Resultaten lassen sich praktische Massnahmen ableiten und umsetzen. 7) CIRS ist auf allen Stufen zu einem wichtigen Werkzeug zur Qualitätsverbesserung geworden.
*(chronologisch für 2005, 2006, 2007)

P92

Transiente Globale Amnesie: nicht so selten

Hutter A., Bächli E.B., Waespe W., Berli R. (Uster, Zollikerberg)

Einleitung: Die Transiente Globale Amnesie (TGA) ist ein klinisches Syndrom, das durch eine plötzliche antero- und retrograde Amnesie bei unauffälligem neurologischen Status und kompletter Remission innert 24 h charakterisiert ist. Die Patienten (Pat) sind zeitlich desorientiert, jedoch durchwegs geordnet in ihrem Verhalten und können komplexe Vorrichtungen ausüben. Die TGA ist für den Pat und dessen Angehörige ein traumatisches Erlebnis. Die Pathogenese ist unklar. Differentialdiagnostisch (ddx) muss die TGA von einem komplex partiellen epileptischen Anfall, einem postiktalen Zustand, einer psychogenen Amnesie, einer cerebralen Durchblutungsstörung und einer medikamentös induzierten Amnesie abgegrenzt werden.
Patienten und Methode: Retrospektive Analyse aller im Schwerpunktspital Uster hospitalisierten Pat zwischen 1/2005–10/2007. Das Spital ist für die Primärversorgung von ca. 160 000 Pat verantwortlich. Unter den 8166 Pat waren 22 mit 23 Episoden einer TGA, die zusammen mit dem Neurologen diagnostiziert wurden. Bei allen erfolgte ein follow up nach 2–22 Monaten.
Resultate: Bei den 22 Pat war das Durchschnittsalter 66 Jahre (Range 58–86), 57% waren Frauen. Ein Pat erlitt ein Rezidiv und wurde erneut hospitalisiert. Die durchschnittliche Hospitalisationsdauer war 2 Tage (Median). Alle 23 Episoden hatten die antero- und retrograde Amnesie, die sich innert 24 Stunden zurückbildete. In 18% trat die TGA nach einer körperlichen Anstrengung, 22% bei einem emotionalen Stress und in 60% konnten keine speziellen Umstände eruiert werden. Bei sämtlichen Pat wurde ein CT und in 3 Fällen zusätzlich ein MRI durchgeführt. In 47% wurde eine Duplexuntersuchung der hirnzuführenden Arterien durchgeführt. Bei keinem wurde primär ein EEG durchgeführt. Bei keinem lag eine medikamentöse Ursache zu Grunde. Risikofaktoren für eine Arteriosklerose bestanden bei 77% (61% art. Hypertonie, 26% Dyslipidämie, 22% Nikotinabusus). Bei allen Pat wurde eine EKG Untersuchung und in 39% wurde eine Rhytmusüberwachung durchgeführt. Im follow up wurde bei 2 Pat ein Rezidiv diagnostiziert, somit erlitten 14% der Pat ein Rezidiv. Dies entspricht einer Inzidenz der TGA von 7,5/100000/Jahr, dies in Übereinstimmung mit der in der Literatur beschriebenen Inzidenz von 5/100 000/Jahr und einer Rezidivrate von 15%.
Schlussfolgerung: Die TGA ist ein Syndrom, das den Internisten der Notfallstationen bekannt sein muss. Die TGA ist nicht selten und die Diagnose kann klinisch gestellt werden.

P93

Documentation of patient's medication at hospital admission: How good are we? Evaluation in patients admitted for elective coronary angiography

Frei P., Huber L.C., Simon R.W., Bonani M., Lüscher T.F. (Zürich)

Objective: Errors in medication might happen at hospital admission when hospital doctors are not adequately informed about a patient's established medication. Here we wanted to assess differences between admission letters from referring practioners, personal medication lists and oral informations provided by the patient at hospital entry.
Methods: The medication of 103 patients who were electively admitted for coronary angiography was assessed. Discrepancies between admission letters, written instructions (personal medication lists) and what patients told about their medication were analyzed. Brand names/generics, dosages and frequencies were noted.
Results: Patients took a mean of 5 ± 3 drugs. 9% of all drugs taken could only be discovered by systematic medication anamnesis, but were not stated in admission letters or medication lists. Only 88% of admission letters reported whether the patient is on any medication (and if yes, on which medication). 23% of all drugs were generics, but 21% of generics were stated as original compounds in the admission letter. Less than 50% of patients taking 4 or more drugs had a written instruction how to take their medication. 76% of patients brought their medication with them at hospital admission which facilitates medication assessment. By comparing data from all three different sources in order to find out the putative established medication, we found that a total of 86 medications were not identical, leaving uncertainties to the hospital doctors how outpatient medication should be continued. Medication was modified in 25% of all patients at hospital discharge.
Conclusion: Instructions for patients taking multiple drugs need to be improved. This might increase compliance and reduce uncertainties about medication at hospital admission, thereby decreasing medication errors in the hospital and allowing useful changes in medication when necessary.

P94

Sarcoïdose et tératome ovarien, nouvelle entité?

Geismann F.I., Masset C., Blondel N., Betticher D. (Fribourg)

Cas clinique: Une patiente de 39 ans est adressée dans le service de gynécologie pour une tumeur de 10cm de diamètre au niveau de l'ovaire droit avec infiltration intestinale, ainsi que des nodules hépatiques, spléniques et pulmonaires suggestifs de métastases. Les mar-

queurs tumoraux ([beta]-HCG, [alpha]-FP, CA125) sont négatifs et colonoscopie et gastroscopie sont normales. Dans ses antécédents, elle déclare être connue pour une toux allergique depuis l'adolescence. Dix huit mois auparavant, la patiente avait présenté une myocardite au décours d'une infection respiratoire. Le bilan cardiologique effectué montrait une dysfonction cardiaque modérée avec des coronaires saines et l'IRM mettait en évidence une myocardite étendue. Un bilan pneumologique comprenant des fonctions pulmonaires complètes avec DLCO et radiographie du thorax était alors normal. Une laparotomie est pratiquée avec annexectomie et biopsie hépatique. L'histologie ovarienne révèle un tératome (kyste dermoïde) sans signe de malignité, et la biopsie hépatique montre des granulomes à cellules épithéloïdes et giganto-cellulaires de type Langhans, avec des infiltrats lymphocytaires, sans nécrose (coloration Ziehl-Neelsen et PCR négatives pour Mycobacterium), compatibles avec une sarcoïdose. Il n'y a pas d'atteinte ophtalmologique ni cutanée. Dans un deuxième temps, une biopsie cardiaque est pratiquée et l'histologie montre elle aussi des lésions compatibles avec une sarcoïdose.
Discussion: L'association entre tumeur germinale et sarcoïdose a été décrite dans plus de 50 cas dans la littérature. Nous rapportons le premier cas d'un tératome ovarien associé à une sarcoïdose. Les granulomes pulmonaires sans adénopathie hilaire ni infiltration interstitielle représentent un stade radiologique III atypique, mais cet aspect de métastatisation diffuse hépato-spléno-pulmonaire est rarement décrit. Seuls 5% des patients souffrant de sarcoïdose ont une atteinte cardiaque symptomatique, cependant ce diagnostic est probablement sous-estimé. Une corticothérapie doit être instituée dans une telle situation et l'implantation d'un défibrillateur devrait probablement être considérée au vu du risque élevé d'arythmies.

P95

Erhöhte Kokain-Spiegel bei Body-packing: Alarmzeichen oder Innocent Bystander?

Fretz G., Traupe T., Senn A., Hofer C., Frick S. (Zürich)

Fallbeschreibung: Eine 18jährige Patientin wurde wegen starker Agitation und Dyskinesien der Gesichtsmuskulatur auf die Notfallstation eingewiesen. BD 116/55 mm Hg, P 79/min. Der restliche Status sowie das Labor war bis auf eine leicht erhöhte CK von 676IU/L normal. Auf der Notfallstation setzte die Patientin 7 Päckchen Kokain ab, worauf die Diagnose des Body packings radiologisch bestätigt werden konnte.

Abb. 1
Nachweis der Body-packs

Klinische Fragestellung: Die qualitative Urin-Analyse war positiv für Kokain. Bei persistierender Verwirrung und schweren Dyskinesien, jedoch normalen Vitalparametern stellte sich die Frage, ob das Kokain im Urin von der Patientin separat eingenommen wurde oder aus einem geplatzten Päckchen stammte. Letzteres hätte eine notfallmässige Operation bedingt [1, 2].
Verlauf: Nach 12 h Überwachungszeit lagen die quantitativen Urin-Analysen vor: der Kokain-Spiegel betrug 1761 ug/l, die Metaboliten waren ebenfalls im hoch-toxischen Bereich (Benzoylecgonin 6204 ug/l, Methylecgonin 1408 ug/l). Ausserdem wurden überraschenderweise hohe Konzentrationen von Diltiazem und seinen Metaboliten im Urin gefunden. Auf Grund der stark erhöhten Kokainkonzentrationen im Serum war die Indikation zur Operation gegeben. Intraoperativ präsentierten sich neben 23 intakten ein teilweise entleertes Päckchen. Die Analyse eines der intakten Päckchens ergab eine Mischung von Kokain und Diltiazem im Verhältnis von 9:1.

Abb. 2
«Geplatztes» Päckchen

Kommentar: Die Beigabe von Diltiazem als Streckmittel zu Kokain soll gelegentlich vorkommen (Wissenschaftlicher Dienst der Stadtpolizei Zürich). In unserem Fall wurde dadurch eine notwendige Operation verzögert aufgrund der irreführenden Klinik. Es scheint, als hätte die Beigabe von Diltiazem die kardiovaskulären Effekte des Kokains unterdrückt [3]. Unseres Wissens ist kein Fall bekannt, bei dem sich eine schwere Intoxikation durch ein geplatztes Body-pack mit einer Kokain-Diltiazem Mischung so atypisch präsentierte.
1. Prognosis of cocaine body-packers. Prost N, Lefebvre A, Questel F, Roche N, Pourriat JL, Huchon G, Rabbat A; Intensive Care Med 2005; 31:955–8.
2. Cocaine-body-packing. Infrequent indication for laparotomy. Schaper A, Hofmann R, Ebbecke M, Desel H, Langer C; Chirurg – Vol. 74, Issue 7, Jul 2003, Pages 626–31.
3. Calcium channel blockers antagonize some of cocaine's cardiovascular effects, but fail to alter cocaine's behavioral effects; Schindler CW, Tella SR, Prada J, Goldberg SR.J Pharmacol Exp Ther. 1995 Feb;272(2):791–8.

P96

Necrobiosis lipoidica eine Präkanzerose?

Gogos G., Gütling M., Pless M., Ballmer P. E. (Winterthur)

Wir präsentieren die Kasuistik einer 62jährigen Patientin, welche uns zur Abklärung von diffusen Abdominalbeschwerden zugewiesen wurde. Eine computertomographische Untersuchung zeigte eine ausgeprägte generalisierte Lymphadenopathie abdominal, retroperitoneal und inguinal beidseits. Der histologische Befund einer Lymphknotenexzision inguinal rechts ergab die Diagnose eines verhornenden Plattenepithelkarzinoms. In der Folge wurde intensiv nach der Herkunft dieser Lymphknotenmetastase gesucht; sowohl anal wie auch im Urogenitaltrakt konnten keinerlei Hinweise auf einen Primärtumor gefunden werden. Die Patientin litt seit 1972 an einer ausgeprägten Necrobiosis lipoidica beider Unterschenkel, seit 1999 traten zunehmend auch Ulzerationen auf. Ein Diabetes mellitus war nicht vorhanden. Gemäss dermatologischer Beurteilung lag der Primärtumor mit sehr hoher Wahrscheinlichkeit im Bereich der exulzerierten Fläche am distalen Unterschenkel rechts. Da beim metastasierendem Plattenepithelkarzinom als einzige Therapieoption eine systemische Chemotherapie in Frage kam, wurde auf eine diagnostische Biopsie im Wundbereich verzichtet. Insgesamt wurden 4 Chemotherapiezyklen mit Cisplatin durchgeführt. Initial zeigte sich ein Ansprechen auf die Therapie mit grössenregredienten Lymphknoten. Im weiteren Verlauf war das Tumorleiden wieder progredient mit neuen ossären Metastasen, sowie paraneoplastischen Lungenembolien. Die Patientin verstarb 6 Monate nach der Erstdiagnose des Plattenepithelkarzinoms. Die Entstehung eines Plattenepithelkarzinoms auf der Basis einer Necrobiosis lipoidica ist extrem selten (A. Stein et al; Plattenepithelkarzinome als seltene Folgeerkrankungen auf kutanem Lichen ruber und Necorbiosis lipoidica. Akt Dermatol 2003;Heft 08/09,V30), weltweit sind sehr wenige Fälle publiziert. Meistens handelte es sich, wie bei unserer Patientin, um die ulzerative Form einer langjährigen Necrobiosis lipoidica.

P97

Vermeintliche Meningeosis carcinomatosa bei Neuroborreliose

Gogos G., Rodic B., Ballmer P. E. (Winterthur)

Wir präsentieren die Kasuistik einer 87jährigen Patientin, welche uns bei neuroradiologischem Verdacht auf Meningeosis carcinomatosa zur weiteren Abklärung zugewiesen wurde. Anamnestisch berichtete sie über ein chronisches lumbales Schmerzsyndrom mit Ausstrahlung ins rechte Bein, sowie über einen seit zwei Monaten aufgetretenen bandförmigen, nicht atemabhängigen Schmerz in der Mitte der Brustwirbelsäule. Dieser zeigte sich therapieresistent auf hochdosierte Analgetika. Seit der Kindheit bestehen eine thorakale Skoliose, sowie zahlreiche Hautknoten an den Extremitäten, wobei die Familienanamnese bezüglich fibromatöser Erkrankungen positiv war. Klinisch fanden sich ausser einer leichten Gangataxie, welche topographisch nicht eingeordnet werden konnte, sowie einem anamnestisch vorbestehendem partiellen Sensibilitätsverlust im Dermatom L5/S1 keine fokalen Defizite. Die thorakalen Beschwerden waren mit einem radikulären/segmentalen Th6/7 Reizsyndrom vereinbar. In der auswärtigen MRT Untersuchung der lumbalen Wirbelsäule liessen sich diverse Kontrastmittel aufnehmende intradurale Knoten entlang der Cauda equina nachweisen, bei welchen vom radiologischen Aspekt her eine Meningeosis carcinomatosa als Verdachtsdiagnose im Vordergrund stand. Die MRT Untersuchung der restlichen Wirbelsäule und des Schädels waren unauffällig. Ein Primärtumor konnte nach ausgiebigem Screening nicht gefunden werden. Auch die mehrfach durchgeführte Liquoruntersuchung ergab keine Anhaltspunkte für maligne Zellen, zeigte jedoch eine lymphozytäre Pleozytose. Sowohl die IgG als auch die IgM Borrelia burgdorferi-Antikörper konnten im Serum und Liquor als reaktiv nachgewiesen werden, weshalb zusammen mit den klinischen Befunden (thorakale Radikulitis) und der lymphozytären Meningitis von einer Neuroborreliose im Frühstadium (Stadium II, Garin-Bujadox-Bannwarth-Syndrom) ausgegangen wurde. Nach einer vierwöchigen intravenösen Therapie mit Ceftriaxon (2 g/24 h) zeigten sich die Schmerzen regredient. Zwei Monate später war die Patientin praktisch beschwerdefrei. Die Aetiologie der intraduralen Knoten bleibt noch offen. Möglicherweise handelt es sich um Schwannome (allenfalls bei einer rudimentären Form einer Neurofibromatose Typ 1), differentialdiagnostisch kämen aber auch kleine Abszesse im Rahmen der Neuroborreliose in Frage. Die geplante MRT Kontrolluntersuchung in drei Monaten wird die Aetiologie hoffentlich klären.

Abb. 1
unklare Knoten 1

Abb. 2
unklare Knoten 2

P98

Liver failure in a patient with phaeochromocytoma crisis

Brauchlin A.E., Rudiger A., Maggiorini M. (Zürich)

We present a 50 year old man with malignant phaeochromocytoma in whom the tumor was first diagnosed and resected at the age of eleven. After years of remission, recurrent disease was diagnosed four years ago. The current history started with somnolence and jaundice. Initial treatment with labetalol failed, and the patient required intubation. For further diagnostics and management, he was transferred to our intensive care unit. On admission, the patient had a blood pressure of 128/76 mm Hg, clammy skin and black toes. A CT-scan showed the large (8 cm in diameter) intraabdominal tumor.
A portal vein thrombus with infarction of the right liver lobe was detected. Laboratory-testing was remarkable for highly elevated liver enzymes, a coagulopathy and lactatemia. A severely depressed left ventricular function of less then 20% was revealed by echocardiography. Albeit normal blood pressure values at this time point, serum norepinephrine-levels were seventy times the upper limit. The patient was anuric, and impaired kidney perfusion was seen by ultrasound. We begun treatment with high-dose intravenous phentolamin and fluids. The peripheral circulation improved, the cardiac index increased from 2,5 l/min/m^2 to 4l/min/m^2 and lactate values normalized within hours. After a day of effective treatment, repeat echocardiography showed recovery to baseline values. With restitution of adequate arterial blood flow, liver function recovered and anticoagulation was initiated for the treatment of the portal vein thrombosis. Under renal replacement therapy, creatinin-levels normalized. The patient was extubated four days after admission. Antihypertensive treatment was changed to a combined oral regimen with doxazosin, carvedilol, lisinopril and nifedipin. However, sufficient blood pressure-control could only be achieved with doses above standard recommendations. A Fluor-Dopa-PET-Scan did not show additional phaeochromocytoma metastasis, and the patient was scheduled for surgical resection of the tumor. Portal vein thrombosis with liver infarction is an exceptional presentation of phaeochromocytoma. We hypothesize that volume depletion and low blood-flow let to this complication. The case highlights the fact, that phaeochromocytoma can present with multiorgan failure. Effective alpha-blocking treatment and fluid-administration are essential in order to maintain the macro- and microcirculation and to prevent further deterioration.

P99

Contribution des colloques «Mortalité & Morbidité» à l'amélioration de la qualité des soins

Carron P-N., Deriaz S., Ribordy V., Hugli O., Lamy O., Waeber G. (Lausanne)

Introduction: La gestion des risques et l'amélioration de la qualité des soins passent par l'identification de situations critiques et par l'analyse de leurs causes. À cet égard, les colloques «Mortalité & Morbidité» (M&M) constituent un extraordinaire outil d'enseignement. A la lumière d'une situation critique, nous présentons la stratégie mise en place dans le service de médecine interne et le centre des urgences, services affiliés dans la prise en charge des patients et la formation des médecins.
Méthode: Des colloques d'une durée d'une heure réunissent mensuellement l'ensemble des médecins des deux services. Un cas concret survenu dans les dernières semaines est présenté par un chef de clinique et discuté avec les participants. Pour dépasser la notion de faute, le secret médical et l'anonymat des intervenants sont garantis. Les facteurs favorisants, ainsi que les moyens permettant d'éviter à l'avenir un incident similaire sont identifiés. En parallèle, les bases théoriques de gestion de risque, de survenue d'erreurs humaines et de travail en équipe sont abordées.
Cas clinique: Un homme de 28 ans est admis aux urgences pour un sevrage éthylique. À l'anamnèse, on relève une consommation d'un litre d'alcool fort par jour, ainsi qu'une hospitalisation aux soins intensifs lors d'un précédent sevrage. Dès l'entrée, il présente une crise convulsive tonico-clonique, répondant rapidement à l'administration de benzodiazépines. Le bilan paraclinique révèle une hypokaliémie, ainsi qu'une hypomagnésémie. L'apparition d'un delirium tremens nécessite l'instauration d'un traitement de lorazepam, puis de clorazepam iv. Le patient présente alors un arrêt cardio-respiratoire sur une torsade de pointes (Fig. 1). La relecture a posteriori de l'ECG confirme un intervalle QT prolongé à 510 msec. L'évolution est favo-

rable après réanimation et correction de troubles électrolytiques.
Discussion: Le risque d'arythmies malignes et en particulier de torsades de pointes est largement décrit lors de sevrages alcooliques compliqués. L'analyse du cas permet d'identifier plusieurs lacunes dans le diagnostic, dans l'identification des critères de gravité et dans la prise en charge thérapeutique (Fig. 2).
Conclusions: Les colloques M&M jouent un rôle essentiel dans le développement d'une véritable culture de l'erreur. En ce sens, ils répondent aux exigences de formation de la FMH et participent à l'acquisition de compétences médicales modernes.

Fig. 1
Torsade de pointes

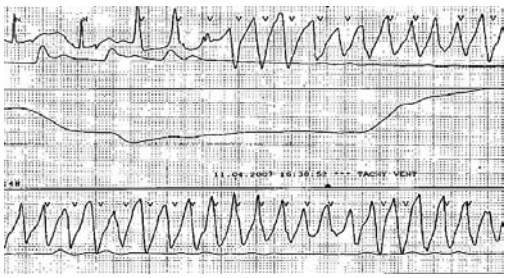
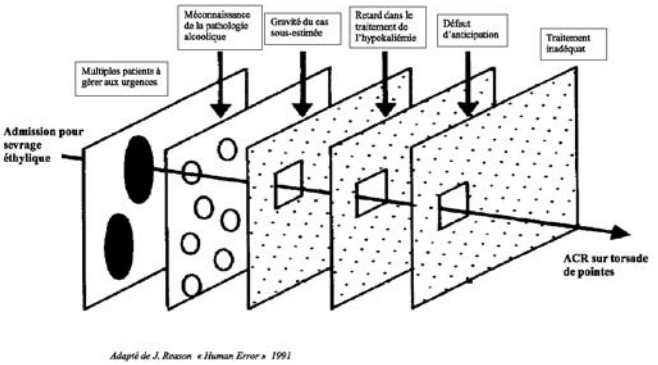


Fig. 2
Trajectoire d'occasion


Méconnaissance de la pathologie alcoolique
Gravité du cas sous-estimée
Retard dans le traitement de l'hypokaliémie
Défaut d'anticipation
Traitement inadéquat
Multiples patients à gérer aux urgences
Admission pour sevrage éthylique
ACR sur torsade de pointes
Adapté de J. Reason « Human Error » 1991

P100

Hartnäckige Doppelbilder – nur endokrine Ophthalmopathie bei M. Basedow?

Vetsch G., Pato U., Fischli S., Lepper S., Loennefors T., Offinger A., Bürgi U., Schiemann U. (Bern)

Wir beschreiben den Fall einer 42jährigen Patientin mit einer gastrointestinalen Infektion Anfang 2007. Im weiteren Verlauf traten Schmerzen am Hals, eine Hyperosmie sowie Doppelbilder und Schwindel auf. Laborchemisch fand sich die Konstellation einer hyperthyreoten Stoffwechsellage mit einem supprimierten TSH (0,04 mU/l) und erhöhten Werten für FT3 (12,1 pmol/l) und FT4 (36,1 pmol/l). Die TSH-Rezeptor-Antikörper (1,9 U/l) und mikrosomalen Antikörper (139 kU/l) waren leicht erhöht. Das MR der Orbitae zeigte eine Schwellung der Mm. recti inferiores. Unter der Diagnose eines M. Basedow mit begleitender endokriner Ophthalmopathie wurde eine Behandlung mit Carbimazol (20 mg tgl.), Propranolol (80 mg tgl.) und Prednison (100 mg tgl.) begonnen. Der klinische Status besserte sich trotz Normalisierung der Laborwerte zunächst jedoch nicht. Die Augenmotilität blieb erheblich eingeschränkt. Die Schilddrüsensonographie war normal, zeigte insbesondere keine für den M.Basedow typische Hypoechogenität des Parenchyms. Neurologischerseits fielen eine Konvergenzschwäche und abgeschwächte Eigenreflexe auf. Das EMG und der Mestinontest waren normal, die Acetylcholin-Rezeptor-Antikörper negativ. Die Anti-GQ1b-Antikörper waren mit einem Titer von >15000 U/l massiv erhöht, so dass wir die Diagnose eines Miller-Fisher-Syndroms stellen konnten. Das Miller-Fisher-Syndrom ist eine seltene Variante des Guillain-Barré-Syndroms und durch das kombinierte Auftreten von Ophthalmoplegie, Ataxie und Hyporeflexie gekennzeichnet. Anti-Glykolipid-Antikörper sind hoch sensitiv für dieses Syndrom (in 85–90% der Fälle nachweisbar), was einen Hinweis auf die Schädigung peripherer Myelinscheiden gibt. Das GQ1b-Epitop wurde u.a. auch in Lipopolysacchariden von Campylobacter jejuni gefunden (Pat. hatte einen reaktiv positiven Titer), so dass man eine entsprechende Infektion als Trigger ansehen kann. Die Therapie erfolgt in schweren Fällen analog zur Behandlung eines Guillain-Barré-Syndroms (Immunglobuline, Plasmapherese). Die Spontanheilungsrate ist jedoch glücklicherweise relativ hoch, wie bei unserer Patientin, so dass keine spezifische Therapie erforderlich war. 4 Monate nach der Hospitalisation waren alle körperlichen Beschwerden verschwunden, die Augenmotilität komplett wiederhergestellt. Auch die thyreostatische Behandlung und Steroidtherapie konnten gestoppt werden.

P101

Monoarticular septic arthritis due to Streptococcus pneumoniae

Karathanasis S., Di Benedetto C., Chimchila Chevili S., Pons M., Bernasconi E. (Lugano)

Septic arthritis due to Streptococcus pneumoniae is rarely reported in modern times. The incidence of pneumococcal septic arthritis in patients with pneumococcal bacteremia is extremely low, ranging from 0.5 to 0.7 percent in three different case series. A 76 year-old man affected by Hodgkins disease (Ann Arbor Classification stage IVB) presented with erythema, swelling and pain of the left ankle. The patient was unable to walk due to the pain that was exacerbated by light palpation. Because of a severe thrombocytopenia an arthrocentesis was not performed. However, in the blood cultures growth of S. pneumoniae was detected. The initial antibiotic treatment with Imipenem i.v. was changed to Ceftriaxone i.v. for a total of four weeks with both clinical and laboratoristic improvement. The second case refers to a 77 year-old man with hypertensive cardiopathy and chronic atrial fibrillation that presented with fever, and chills in the last 48 hours. He developed a swelling of the right knee with local erythema and pain when moving. Blood cultures were taken and empirical treatment with Ceftriaxone was immediately started. One day later an arthrocentesis was performed. S.pneumoniae grew in the blood cultures, but not in the synovial fluid. However, eubacterial polymerase chain reaction (16S rDNA directed PCR) was positive and DNA sequencing confirmed the presence of S.pneumoniae in the synovial fluid. Treatment with Ceftriaxone i.v. for five weeks combined with a repeated surgical drainage resulted curative. S. pneumoniae can cause suppurative joint infections, being the knee, wrists, ankles and hips more commonly involved. One review of 190 cases of pneumococcal septic arthritis that occurred over 40 years noted that the majority of cases were monoarticular, but polyarticular involment occurred in 36 percent of cases. Even in the absense of a clinically apparent focus of pneumoccoccal infection, e.g. pneumonia, S. pneumoniae should be considered as a possible cause of suppurative arthritis.

P102

Der Arbeitgeber als Ursache einer Blutdruckkrise

Signorell L., Wertli M., Weber M., Gubler J. (Winterthur)

Fallpräsentation: Zuweisung eines 44jährigen Patienten bei schwer einstellbarer, arterieller Hypertonie unter ausgebauter Medikation. Ein obstruktives Schlafapnoesyndrom wird behandelt, ebenso sind sekundäre Ursachen (Nierenarterienstenose, Endokrinopathien) weitgehend ausgeschlossen worden. Hinweise auf weitere sekundäre Hypertonieursachen wie NSAR-Einnahme, Äthyl- oder Drogenabusus oder eine Malcompliance bestehen nicht. Als Endorganschaden zeigt sich eine hypertensive Herzerkrankung mit erhaltener linksventrikulärer Funktion. Eine aussagekräftige Ergometrie (Doppelprodukt 2,8) zeigt keine Belastungshypertonie. Die nachfolgende 24 Stunden Blutdruck (24h-BD)-Messung zeigt eine erhebliche Hypertonie Grad 2–3 mit einer hypertensiven Gefahrensituation um

10:40 Uhr von 221/118 mm Hg (Tabelle 1: Messung 1). Die Befundbesprechung mit dem Patienten ergibt, dass ihm genau zu diesem Zeitpunkt die Stelle gekündet wurde! Es liegt somit eine deutliche vegetative Komponente vor, welche die Durchschnittswerte der Messung deutlich beeinflusst. Bestätigt wird dies in einer Verlaufsmessung (Tabelle 1: Messung 2), welche unter äquivalenter Therapie deutlich niedrigere Blutdruckwerte demonstriert.
Diagnose: Sympathikotone Reaktion bei Dysstress als Fehlerquelle der 24h-BD-Messung.
Diskussion: Bei schwer einstellbarer arterieller Hypertonie ist eine 24h-BD-Messung indiziert. Sie ermöglicht die Entdeckung weiterer Ursachen (wie Malcompliance, Fehlmessungen, Sprechstundenhypertonie) sowie die Dokumentation des Schweregrades. Die differenzierte Auswertung der Messung ist jedoch von zentraler Bedeutung. Wie im obigen Fall beschrieben, haben bekannte Stressoren wie Arbeit, Sport (inklusive Fussballspiel am Fernsehen) und die Schlafqualität einen wesentlichen Einfluss auf das Blutdruckverhalten. Ebenso können für Patient und Arzt unerwartete Ereignisse grosse Auswirkungen haben.

Tabelle 1

Tabelle 1: Werte der 24- Stunden Blutdruck-Messungen		
Datum	Messung 1: 05/2007	Messung 2: 06/2007
	Durchschnitt (min - max)	Durchschnitt (min - max)
BD systolisch (mmHg)	175 (136 - 221)	139 (98 - 179)
BD diastolisch (mmHg)	104 (66 - 124)	84 (44 - 122)
Hf (/min.)	70 (56 - 94)	74 (63 - 90)
Medikamente:	Wirkstoff (mg/Tag)	Wirkstoff (mg/Tag)
	Lisinopril (40)	Candesartan (16)
	Bisoprolol (10)	Bisoprolol (10)
	Torasemid (10)	Torasemid (20)
	Hydrochlorothiazid (12,5)	Hydrochlorothiazid (25)

P103

A medical mystery – a patient with malaise, headache and altered mental state after loss of consciousness with need for short resuscitation

Marsteller I., Hagara D., Massari I., Bernasconi E., Pons M. (Lugano)

Emergency medical services make efforts to improve quality and promptness of preclinical care as well as trying to fix as early as possible a probable diagnosis. Once arrived in hospital, the quality of care is crucial for the clinical course and outcome of every patient. We report the clinical case of a 61-year-old man who was admitted to our emergency department after loss of consciousness with need for short resuscitation outside the hospital. At arrival he presented with malaise, headache and somnolence. Past medical history was uneventful. We noted the absence of allergies and regular drug intake. The patient took two tablets of Aspirin prior to admission. While cardiovascular risk factors were absent, he admitted having drunk little alcohol the day before. Initially the patient showed psychomotor retardation with amnesia and referred vertical diplopia. The objective neurological status and general physical examination showed no abnormalities, haemodynamics were always stable. ECG, chest X-ray radiograph and a cerebral CT scan revealed no pathologic findings. There were no diagnostic hints in the routine laboratory tests. The analysis of cerebro-spinal fluid showed no abnormalities. The patient was hospitalised for monitoring of suspected transient ischemic attack. Urine-drug-screening was only positive for benzodiazepines, on enquiry the patient reported having taken Lorazepam 5 mg the night before in order to fight job-related stress. Doppler ultrasound of jugular and cervical arteries as well as cerebral MRI was negative. The clinical course was favourable. Stumbling on the patient's comment about work-related stress with implications on his family it was offered a psychiatric consultation that he accepted willingly. In this conversation the patient, now bright and lucent, revealed having provoked most of his symptoms in order to obtain a complete medical "check-up" of "highest quality" that he would not have had with his general practioner. The specialist did not diagnose any psychiatric disease. The patient was discharged on the fourth day after admission. In conclusion, this report shows the difficulties we had in providing correct diagnosis despite explicit medical history, physical examination, neurological consultations and extensive technical tools. A part from the mystery unravelled, possible implications for medical reasoning, health policy and for the doctor-patient relationship are discussed.

P104

Decision making capacity in a general internal medicine ward: competence or not? That's the question

Fassassi S., Bianchi Y., Stiefel F., Waeber G. (Lausanne)

Background: Assessment of capacity to consent to treatment is an important medical, legal and ethical issue in daily clinical practise.
Objective: To compare the results of an evaluation of patients' competence by members of the medical team, a specific tool (Silberfeld's score) and a psychiatric expert.
Method: Over a 3 months period all of the 265 potentially eligible patients admitted within the first 72 hours in a acute care setting of a general internal medicine unit were prospectively evaluated for their decision making capacity (competence). For each enrolled patient a research fellow (YB) gathered the different evaluations of the medical team (junior doctor, senior doctor, nurses and referring general practitioner) and applied the Silberfeld and the MMSE (Mini Mental Status Examination) and a psychiatrist (SF) assessed the patient independently with regard to his competence.
Results: 108 (40.8%) patients were excluded: 38 (14.4%) because of evident incompetence (patients were unconscious or severely cognitively impaired) and 70 (26.4%) were excluded for other reasons (patient refusal, hemodynamic instability, language disabilities, etc.). Of the 157 patients enrolled, 14 were considered incompetent by the psychiatrist. This summs up to a total of 52 out of 265 inpatients (19.6%) who had an impaired decision-making capacity. Agreement between the psychiatric evaluation and the Silberfeld questionnaire was poor (kappa 0.249) with a sensitivity of 35.7% and a specificity of 91.6%. Experienced clinicians showed higher agreement (sensitivity of 57.1% and specificity of 96.5%) with the psychiatric evaluation. The association of all of the treating team members showed even higher sensitivity (78.6%).
Conclusions: Clinicians should be aware and trained to assess patient's competency. This study demonstrated that a specfic tool like the Silberfeld is less useful than an interdisciplinary evaluation by clinicians. Given the high percentage of incompetent patients admitted to General Internal Medicine, clinicians' training should include the evaluation of competency in order to fullfill current medico-legal requirements.

P105

Klossige Sprache und schwere Augenlider am Abend

Stempfle V., Bertschy S., Donati F. (Biel)

Eine 72jährige Patientin stellte sich auf unserer Medizinischen Notfallstation wegen Sprechproblemen bedingt durch «eine schwere Zunge» seit 14 Tagen vor. In den letzten Tagen waren zusätzlich Probleme beim Kauen und Schlucken aufgetreten, ausserdem eine heisere Stimme und seit 2 Tagen eine Lidschwäche des linken Auges. Die Kau/Schluckprobleme hatten dazu geführt, dass sie in den letzten Tagen nur noch flüssige Nahrung zu sich nehmen hatte können und Gewicht abgenommen hatte. Die persönliche Anamnese war bland, ausser ihres Alters hatte sie keine kardiovaskulären Risikofaktoren. In der klinischen Untersuchung fiel eine kachektische Patientin auf. Die Lidspalte links war enger als rechts, eine fragliche Mundastschwäche links, leichte Dysarthrie bei verlangsamter Zungenmotilität, erhaltene Augenmotilität, die linke Pupille war diskret kleiner gegenüber rechts. Die kardiopulmonale Untersuchung und der restliche Neuro-Status waren unauffällig. Bei Verdacht auf Hirnstammpathologie veranlassten wir ein MRI des Schädels inklusive Angiographie, welches ausser einer vaskulären Leukenzaphalopathie keine pathologischen Befunde zeigte. Wegen diskreter Horner-Symptomatik links dachten wir ausserdem an eine Raumforderung intrathorakal; im CT-Thorax gab es keine Hinweise hierfür. Während der Abklärungszeit auf der Notfallstation (es wurde Abend) kam es zu deutlicher Verschlechterung der Symptomatik: die Sprache wurde klossig, die Patientin konnte ihren Speichel kaum mehr schlucken und ihre Augenlider beidseits kaum mehr heben. Bei dieser Dynamik mit beobachteter Verschlechterung der Beschwerden am Abend kam differentialdiagnostisch eine Myasthenia gravis in Betracht. Nach probatorischer Gabe von Pyridostigmin kam es zu prompter Verbesserung der Symptomatik. Weitere Abklärungen zeigten positive Anti-Acetylcholin-Antikörper, womit die Diagnose einer okulo-bulbären Myasthenia gravis gesichert werden konnte. Einige Monate nach Therapiebeginn mit Pyridostigmin und zusätzlich Steroiden ist die Patientin beschwerdefrei. Der relativ häufige Beschwerdekomplex aus Dysarthrie vergesellschaftet mit Schluckproblemen auf einer medizinschen Notfallstation wurde in diesem Fall durch eine okulo-bulbäre Form der Myasthenia gravis erklärt.

P106

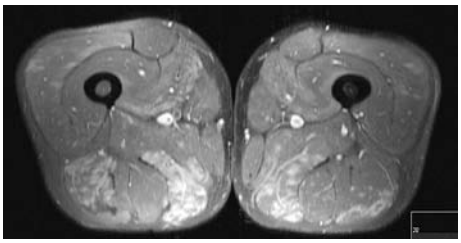
Muskelschmerzen als Erstsymptom einer disseminierten Sarkoidose

Douleur musculaire, le premier symptome d'une sarcoïdose disséminée

Muscle pain as first sign of a disseminated sarcoidosis

Müller C., Knudsen L., Nicod L.P., Schiemann U. (Bern)

Hintergrund: Die disseminierte Sarkoidose mit klinisch manifester muskuloskelettaler Beteiligung ist relativ selten. In der Literatur geht man von 0,5% aller Sarkoidosefälle aus.
Fallbeschreibung: Wir berichten über einen 39jährigen Patienten mit Schmerzen der Schultergürtel- und der proximalen Oberschenkelmuskulatur beidseits, trockenem Husten sowie Gewichtsverlust von 6 kg in 6 Monaten. Histologisch wurde eine Sarkoidose im Muskelgewebe des Oberschenkels sowie im Lungenparenchym nachgewiesen. Aufgrund weiterer klinischer, laboranalytischer sowie bildgebender Untersuchungen vermuteten wir eine disseminierte Sarkoidose mit Beteiligung von Myokard, Lunge, Lymphknoten, Augen, Milz, Leber, Niere und Muskel. Zudem fand sich eine Hyperkalzämie und Hyperkalzurie. Unter Therapie mit Glucocorticoiden und Mycophenolatmofetil zeigte sich im Verlauf eine Verbesserung des Allgemeinzustandes und der Lungenfunktion (Vitalkapazität) mit Regredienz bis Normalisierung vor Therapiebeginn pathologischer Laborparameter.
Konklusion: Bei Vorliegen einer Myopathie muss bei zusätzlichen Hinweisen auf eine Systemerkrankung differentialdiagnostisch eine Sarkoidose erwogen werden. Für die Sicherung der Diagnose ist die Histologie mit Nachweis nicht-verkäsender Granulome wegweisend.
Schlüsselwörter: Myositis, disseminierte Sarkoidose
Abb. 1
MRI Oberschenkel



P107

Schmerzhafte Ophthalmoparese: Tolosa-Hunt Syndrom

Semadeni G.-M., Rodic B., Löschhorn Ch., Ballmer P. E. (Winterthur)

Fall: Wir berichten über den Fall einer 45jährigen Frau mit bekannter Migräne ohne Aura, die einen akuten retroorbitalen Kopfschmerz rechts mit im Verlauf zunehmend aufgetretenen Doppelbildern und Ptosis rechts entwickelt hat. Die neurologische Untersuchung ergab eine partielle externe und interne Oculomotoriusparese des rechten Auges mit ipsilateraler Mitbeteiligung des N. ophthalmicus und fraglich auch des N. opticus, bei gleichzeitig bestehender ausgeprägter Schmerzsymptomatik des Auges bei Bewegung. Die morphologische Evaluation des zentralen Nervensystems mittels Hirn-Kernspintomographie (MRT) und CT-Angiographie schloss einen parasellären Kompressionsprozess aus. Die Liquoranalyse zeigte eine leichte aseptische entzündliche Reaktion ohne Nachweis einer viralen, atypischen oder bakteriellen Infektion bzw. einer autoimmunen entzündlichen Reaktion mittels ergänzenden Laboruntersuchungen. Über Ausschlusskriterien wurde die Verdachtsdiagnose eines Tolosa-Hunt Syndroms gestellt und eine Steroidtherapie mit Prednison 1 mg/kg KG/Tag begonnen. Innerhalb von 72 h kam es zur eindeutigen Schmerzreduktion, nach 5 Tagen zeigte sich die Ophthalmoparese rückläufig. In den folgenden Wochen wurde die Prednisondosis systematisch reduziert und 12 Wochen nach Beginn der Therapie abgesetzt. Zum Zeitpunkt der kranialen MRT-Kontrolluntersuchung, 4 Monate nach Beginn der Steroidtherapie, waren die Schmerzen und die Augenmuskelparesen vollständig verschwunden, der intrakranielle Befund war unverändert normal.
Diskussion: Die Differentialdiagnose einer schmerzhaften Ophthalmoparese ist sehr umfassend und beinhaltet zahlreiche Entitäten inklusive neoplastische, vaskuläre, infektiöse und nicht-infektiöse entzündliche Prozesse. Eine seltene Ursache mit negativer kranialer Bildgebung ist das Tolosa-Hunt Syndrom. Dabei handelt es sich um eine entzündliche Erkrankung der Fissura orbitalis superior und des Sinus cavernosus unklarer Aetiopathogenese, klinisch präsentiert durch eine unilaterale schmerzhafte Parese der Hirnnerven III, IV, VI und des N. ophthalmicus. Der Verlauf ist spontan rückläufig mit Rezidivneigung. Die Diagnosesicherung erfordert jedoch immer umfangreiche Untersuchungen, um eine sekundäre Ursache eines ophthalmoplegischen Kopfschmerzes auszuschliessen.

P108

Prevalence and time-course of acute mountain sickness in adolescents after rapid ascent to 3'450 m

Bloch J., Duplain H., Rimoldi S., Stuber T., Kriemler S., Allemann Y., Sartori C., Scherrer U. (Lausanne, Bern, Basel)

Facilitated by modern transportation, increasing numbers of children and adolescents are visiting high-altitude tourist destinations. Acute mountain sickness (AMS) is a frequent and debilitating complication of high-altitude exposure, but there is little information on the prevalence and time course of AMS in children and adolescents after rapid ascent by mechanical transportation to 3500 m, an altitude at which major tourist destinations are located. We, therefore, performed serial assessments of AMS (Lake Louise Score, LLS) in 48 healthy non-acclimatized adolescents with no previous high-altitude experience (mean ± SD age, 13.7 ± 0.3 yrs; 20 girls and 28 boys) 6, 24, and 48 hrs after arrival at the Jungfraujoch high-altitude research station (3450 m) reached after a 2½ hr ascent by train. The major new finding was that the prevalence of AMS during the first 3 days at no moment of time was greater than 25%. The incidence of AMS was similar in both genders and declined steadily during the stay (17% after 24 hrs, 8% after 48 hrs). None of the subjects had to be evacuated to lower altitude and symptoms responded well to symptomatic treatment. In conclusion, after rapid ascent to high altitude, the prevalence of AMS in adolescents is relatively low, the clinical manifestations are benign and if present, resolve rapidly. These findings suggest that for the majority of healthy non-acclimatized adolescents, travel to 3500 m is safe and pharmacological prophylaxis for AMS may not be needed.

P109

What is the impact of an interactive course with detailed feedback on the clinical skills in musculoskeletal medicine of fourth year medical students?

Perrig M., Berendonk Ch., Hess R., Beyeler Ch. (Bern)

Background: Basic examination skills of the musculoskeletal system (MS) are essential. Yet, many studies have demonstrated a low level of clinical competence in MS, but only few studies looked at measures to improve.
Aims: To assess the immediate and long-term impact of an interactive course with formative feedback on the examination and interpersonal skills of the MS.
Methods: Four consecutive groups with a total of 26 (out of 154) fourth year medical students attended their 8 weeks clerkship in internal medicine. Two groups (14 students) were randomly assigned to the intervention (INT) of a 6x1 hour practical course of the MS (interactive hands on examination of real patients; systematic, detailed feedback to each student by the teacher and the peers). Two groups (12 students) took part in the regular clerkship clinical activities only and served as controls (CO). In all four groups clinical skills (CS) were assessed in an OSCE like station on a 4-point Likert scale [total of 9 items] by two independent raters at the beginning (t0), at the end (t1) and 5-12 months after (t2) the clerkship. They included musculoskeletal examination skills (MSES) [7 items: inspection, palpation, global movement tests, active and passive joint movements, trigger tests and comments on physical findings] and interpersonal skills (IPS) [2 items: patient communication and behaviour]. Statistical analyses included Mann-Whitney and Wilcoxon tests.
Results: All 26 students completed t0 and t1 tests. 13 students

(6 INT, 7 CO) participated in the t2 test. At baseline t0 there were no detectable differences between the INT- and CO-students for CS, MSES and IPS (p = 0.78, p = 0.67 and p = 0.94, respectively). At the end of the clerkship and several months later the CO-students showed no significant changes of their CS, MSES and IPS (t1 p = 0.24, p = 0.56 and p = 0.09; t2 p = 0.50, p = 0.50 and p = 0.52, compared to t0). In contrast, the INT-students showed significantly improved CS, MSES and IPS at the end of the clerkship (t1 p = 0.005, p = 0.009 and p = 0.003) and even several months later for CS and MSES, but not for IPS (t2 p = 0.03, p = 0.03 and p = 1.0, compared to t0).
Conclusions: Specific interactive clinical skills courses with feedback in addition to regular clinical activities on the ward improve CS, MSES and IPS immediately after the teaching, as well as CS and MSES several months later. We conclude that supplementary systematic clinical teaching activities are worth the additional effort.

Figure 1
Results

RESULTS: mean (SD), * p< 0.05 compared to t_0

Time	CS		MSES		IPS	
	CO	INT	CO	INT	CO	INT
t_0	3.13 (0.32)	3.13 (0.37)	3.07 (0.37)	3.09 (0.39)	3.33 (0.34)	3.29 (0.54)
t_1	3.22 (0.24)	3.50 (0.21)*	3.12 (0.26)	3.39 (0.26)*	3.58 (0.34)	3.88 (0.16)*
t_2	3.34 (0.48)	3.64 (0.26)*	3.37 (0.47)	3.67 (0.23)*	3.25 (0.52)	3.54 (0.53)

P110

Histoire clinique: Fistulisation d'un anévrisme de l'aorte abdominale dans une veine rénale

Faucherre M., Lehmann B., Haftgoli N., Menth M., Hayoz D., Gaude J. (Fribourg)

Une patiente de 54 ans, connue pour hypertension et obésité (IMC à 34 kg/m^2), se plaint d'une dyspnée NYHA III et d'oedèmes des membres inférieurs apparus progressivement. Les investigations en ambulatoire consistent en un électrocardiogramme qui met en évidence une tachycardie sinusale avec bigéminisme ventriculaire permanent et une échocardiographie qui montre une dilatation des oreillettes, une hypertrophie ventriculaire concentrique gauche et une hypertension artérielle pulmonaire à 40 mm Hg. En l'absence d'amélioration clinique sous diurétiques et béta-bloquants, la patiente est adressée aux urgences. Au status, on note des hématomes au niveau des bras, une décompensation cardiaque globale et un souffle abdominal. Le bilan sanguin montre une coagulation intravasculaire disséminée, une perturbation des tests hépatiques et une insuffisance rénale aiguë. L'échographie révèle un anévrisme de l'aorte abdominale (AAA) sous-rénal d'un diamètre de 4,2 cm et, postérieurement à ce dernier, une structure vasculaire dans laquelle le doppler capte un signal pulsatile. Le scanner abdominal montre une fistule entre la partie postérieure de l'anévrisme de l'aorte et la structure vasculaire susmentionnée correspondant à une veine rénale gauche. Cette fistule entre l'AAA et la veine rénale est responsable de cette défaillance multiorganique. La patiente bénéficie en urgence d'une intervention chirurgicale comprenant: un pontage de l'AAA par un tube droit et une ligature de la veine rénale gauche rétro-aortique permettant l'exclusion de la fistule. Une étude rétrospective? d'un institut italien de chirurgie générale et cardio-vasculaire a décrit le site de rupture de 373 cas d'AAA (opérés entre 1965 et 1992). En conclusion, les ruptures se font principalement au niveau du rétropéritoine (79,09%) et, plus rarement, dans le péritoine (12,06%), les veines abdominales majeures (6,97%) et le tractus intestinal (1,88%). Ce cas clinique est d'autant plus intéressant que la rupture de l'AAA s'est faite dans une veine rénale rétro-aortique. Il rappelle aussi l'importance du status qui a permis de poser précocement le diagnostic et de diminuer ainsi le risque opératoire. En effet, la prise en charge chirurgicale est le traitement de choix; la présence d'un état de choc pré-opératoire augmente le taux de mortalité [1].
1 J Cardiovasc surg 1993;34:39–47.

P111

Stress during a simulated medical emergency

Hunziker S., Tschan F., Balestra G., Legeret C., Schumacher C., Semmer N., Hunziker P., Marsch S. (Basel, Neuchâtel, Bern)

Being involved in a medical emergency may be a stressful experience for health-care workers. We aimed to assess subjective and objective stress experienced during a scenario of simulated witnessed cardiac arrest. Teams composed of three healthy volunteers (medical students) each participated. After the simulation participants rated the degree of stress and the perceived realism of the scenario on a 10 point likert scale and indicated their emotions using a questionnaire that measures 18 distinct emotions categorised on a intensity scale from 1–5 (emotional wheel). Using Holter monitoring electrocardiographic data were obtained from one participant of each team. 120 medical students participated (37 male, median age 24 years). The mean maximum and minimal heart rates (bpm) were 114 (SD 16) and 70 (SD 8.5). 37% of the students showed significant dynamic ST-segment alterations with relevant J-Point-elevations (>0.1 mV) or T-wave alterations (depressions greater than or equal to 1.0 mm). The most relevant initial motion was concerns/distress (mean 4 out of 5). After the manikin was "rescued" the experience of alleviation (4 out of 5) dominated. The median perceived stress and the median perceived realism of the scenario were at 8 and 9 out of 10 respectively. Conclusions: A simulated medical emergency with a high perceived realism caused substantial subjective stress. Stress was associated with significant alterations in ST-segments in a high proportion of young and healthy participants. The perceived emotional (di-)stress is maximal during the initial phase of high uncertainty easing off after the successful handling of the event. Further studies are required to elucidate the impact of the stress of health-care workers on their performance in medical emergencies.

P112

Resultate einer Befragung niedergelassener Ärzte zum Einfluss der Wirtschaftlichkeitsverfahren auf die ärztliche Berufsausübung

Foglia R., Schaufelberger H., Uhr M., Mainieri F., Bernasconi O., Battaglia E., Pedrazzoli J., Fontana P., Cerny A. (Lugano, Paradiso)

Hintergrund: Das Bundesamt für Gesundheit hat die Kontrolle der Wirtschaftlichkeit wie sie im Artikel 56 des KVG vorgesehen ist, dem Dachverband der Krankenversicherer santésuisse übertragen. Die Umsetzung dieser Kontrollfunktion wurde in den Kantonen unterschiedlich gelöst und erfolgte in der Regel durch Einsetzung einer paritätischen Kommission zusammengesetzt aus Vertretern der Krankenkassen und der Ärzteschaft. Im Kanton Tessin waren in den letzten Jahren eine unbekannte aber vermutlich hohe Anzahl Wirtschaftlichkeitsverfahren aussergerichtlich abgewickelt worden. Im Jahre 2007 war zudem eine besonders hohe Anzahl von neuen Wirtschaftlichkeitverfahren ausgelöst worden was zu einer Verunsicherung der Ärzteschaft führte. Um eine genauere Analyse des numerischen Umfangs aussergerichtlicher Verfahren machen zu können und um den Einfluss derselben auf das ärztliche Verhalten zu untersuchen wurde eine Umfrage bei den niedergelassenen Ärzten im Tessin durchgeführt.
Methodik: An 519 niedergelassene Aerzte wurde ein Fragebogen verschickt mit folgenden Fragen: «Mussten Sie jemals Zahlungen an santésuisse Ticino im Rahmen eines aussergerichtlichen Wirtschaftlichkeitsverfahrens machen?» und «Fühlen Sie sich, in der aktuellen Situation im Tessin frei, nach Wissen und Gewissen zum Wohle Ihrer Patienten als Arzt zu arbeiten?» Die Fragebogen wurden verschickt und die eingegangen Antworten durch einen Notar ausgezählt und analysiert.
Resultate und Diskussion: Die Umfrage ist zum Zeitpunkt der Einreichung des Abstracts noch nicht abgeschlossen: bis zum 13.1.08 sind 196 der 519 verschickten Fragebogen eingegangen. Die definitive Zahl und die Analyse der Antworten werden am Kongress präsentiert werden. Limitationen der gewählten Methodik sind der fehlende Vergleich mit Aerzten aus anderen Regionen und die Tatsache dass nur zwei Fragen gestellt wurden, Faktoren welche eine detaillierte Analyse der Problematik erschweren. Die Umfrage und die dabei gewonnen Erkenntnisse sollen ähnliche Untersuchungen in anderen Teilen unseres Landes anregen und eine breitere Diskussion des Spannungsfeldes um Artikel 56 des KVG auslösen.

P113

Caspofungin (CSP) for prophylaxis (Px) of intraabdominal candidiasis (IC) in high-risk surgical patients (Pts): a pilot study

Senn L., Eggimann P., Ksontini R., Pascual A., Bille J., Calandra T., Marchetti O. (Lausanne)

Background: We have previously shown that 30–40% of surgical Pts with recurrent gastrointestinal perforation/anastomotic leakage, or acute necrotizing pancreatitis develop IC (Lancet 1989, 2:1437). These Pts benefit of fluconazole Px (Crit Care Med 1999;27:1066). A corrected Candida colonization index (CCI) ≥0.4 is a major risk factor for IC (Ann Surg 1994;220:751). CSP, a new therapy for IC including azole-resistant Candida spp., may be used for Px of IC.
Objective: To conduct a non-comparative pilot study on the efficacy and safety of CSP for Px of IC in high-risk surgical Pts.
Methods: Inclusion criteria: age >18, surgery for recurrent gastrointestinal perforations/anastomotic leakage or acute pancreatitis. Exclusion criteria: documented IC, fluconazole Px. CSP Px (70 mg, then 50 mg/day) was given until resolution of the surgical condition. Candida colonization was monitored 1x weekly at ≥3 sites and the CCI calculated. Success was defined by the absence of IC during CSP Px. Occurrence of CSP-related SAE was recorded.
Results: 19 Pts were enrolled: 16/3 males/females, median age 69 (range 40–84). Underlying surgical conditions were: recurrent gastrointestinal perforation/anastomotic leakage (n = 16), acute pancreatitis (n = 3). At study entry, 14 (74%) Pts were in the ICU (median Simplified Acute Physiology Score II: 45, range 31–65), 19 (100%) received antibacterial therapy and 17 (89%) were colonized with Candida (C. albicans in 69%; CCI ≥0.4 in 1/17 case, 5%). Median duration of CSP Px was 16 days (range 4–46). During CSP Px, 17 (89%) Pts remained colonized (C. albicans in 68%), but 0/17 developed a CCI ≥0.4. CSP was successful for prevention of IC in 18 (95%) Pts. Among 5 deaths, none was attributed to IC. No severe CSP-related SAE requiring discontinuation of Px occurred.
Discussion: The results of this pilot study suggest that caspofungin is efficacious and safe for prophylaxis of intra-abdominal candidiasis in high-risk surgical patients.

P114

Chickenpox outbreak within a vulnerable population living in crowded conditions

Bodenmann P., Vaucher P., Zanetti G., Masserey E., Cometta A., Daher O., de Vallière S. (Lausanne, Yverdon-les-Bains, Sainte-Croix)

Objectives: Describe how to manage an index case of chickenpox in a Centre for Asylum Seekers (CAS).
Case: The index patient, a 33-year old male Eritrean asylum seeker living in a CAS in Switzerland, was hospitalised with fever, rash, and tachypnea. He was diagnosed with disseminated varicella zoster virus (VZV) infection and AIDS. The case was reported to the public health department.
Epidemiological follow-up: Secondary cases were to be isolated and serology performed on all asymptomatic Eritrean adults. Two of 44 individuals were negative for prior VZV infection. Six secondary cases, one adult and five children, manifested between days 14 and 23. Transfers to and from the centre were suspended. All residents (n = 124) and staff received information on VZV; all persons at risk were screened for VZV antibodies. Thereafter, VZV sero-negative adults were tested for HIV test and pregnancy, as appropriate. VZV serologies of adult asylum residents were positive in 107 of 111 (96.4%) persons. Ten of the 13 children had no previous VZV infection. One woman was diagnosed pregnant and abortion was induced. All adults were HIV negative. Of the 14 sero-negative residents, only one of the three vaccinated adults did not develop chickenpox within the month (attack rate = 92.9%). Residents were to move freely again. Surveillance was organised, having nurse practitioners from centres report all new cases. Three independent cases were reported from two other centres during the next six months.
Discussion: Asylum seekers are at higher risk for epidemics and for severe varicella. Once a case is identified, these risks should be evaluated. Reviewing the country of origin's immunization policies, reported regional outbreaks, and sero-negative prevalence can be difficult, as there are no international surveillance systems for VZV. This is not true for most other vaccine-preventable diseases. Screening all asylum seekers exposed to VZV is time consuming and inefficient for prophylactic therapy. Our experience suggests a framework for controlling transmission of VZV or other vaccine-preventable disease in CAS: 1) help the staff recognise an index case quickly; 2) isolate the index case during the contagious period and until risk analysis has been done; 3) investigate whether other residents are at high risk within the next 48h (pregnancy, HIV, immunisation coverage charts); and 4) "wait and see" or eventually focus screening on high risk populations.

P115

Cutaneous vasculitis due to Ciprofloxacin

Maunz G., Zimmerli W. (Liestal)

Introduction: Systemic vasculitis is a rare disease with a broad differential diagnosis. We describe 2 patients in whom cutaneous vasculitis appeared during ciprofloxacin treatment and gradually disappeard after stopping.
Case 1: A 68-y-old man with a hematogenous total knee arthroplasty-associated infection due to S. aureus was treated with iv-flucloxacillin for 2 weeks, and then switched to oral ciprofloxacin plus rifampicin. Seven days later, an erythematous palpaple purpuric rash appeared at both legs. One week later, vasculitis with necrotic skin lesions was clinically confirmed by a dermatologist and both antibiotics stopped. Despite further treatment with flucloxacillin, and later with fusidic acid plus rifampicin, all lesions gradually healed.
Case 2: A 74-y-old man with a vascular prosthesis-associated infection due to S. aureus was treated with iv-flucloxacillin. Two weeks later, ciprofloxacin was added because of a nosocomial urinary tract infection due to Klebsiella pneumoniae. Eight days later, hemorrhagic lesions, palpaple purpura and erythema exsudativum multiforme appeared. Remembering the former case, ciprofloxacin was immediately stopped, and the lesions gradually disappeared despite continuous flucloxacillin therapy.
Comment: Both cases had clinically confirmed vasculitis. Vasculitis has been observed during infection such as chronic hepatitis C, endocarditis, bacteremia due to meningoccci and gonococci, as well as other chronic infections. The mechanism of infection-associated vasculitis is vascular inflammation due to local immune complexes. Our patients had both severe S. aureus infection. However, infection could be ruled out as cause of the cutaneous vasculitis, since in both cases appearance and diappearance strictly correlated with ciprofloxacin use. In both cases there was no evidence of renal involvment. Drug-induced immune-complex vasculitis is a small-vessel vasculitis involving postcapillary venules and arterioles. About 10 cases of ciprofloxacin-associated cutaneous and/or renal vasculitis have been published. However, this adverse event must be more frequent in view of our 2 cases within 6 years. Clinicians should be aware of quinolone-associated hypersensitivity vasculitis, because continuation of ciprofloxacin therapy has reported to be fatal.

P116

Invasive mold infections in non-neutropenic patients in a tertiary care hospital: an 11-year postmortem analysis

Imhof A., Gläser C., Schaer D.J., Schoedon G., Schneemann M. (Zürich)

Objectives: Invasive mold infections (IMI) are an important and increasing cause of morbidity and mortality in hospitalized patients.
Methods: To investigate the incidence of IMI and underlying diseases in non-neutropenic patients hospitalized in a tertiary care hospital, all protocols of autopsies performed during an 11-year period (1997–2007) were reviewed.
Results: This retrospective analysis yielded 53 cases of IMI. There were 37 males and 16 females. Median age was 60 years (range 24–85). 50 cases with IMI and 3 patients with aspergilloma were diagnosed. The most frequent isolates in patient with IMI were Aspergillus species (96%) followed by Fusarium species (2%), and Scedosporium apiospermum (2%). Fungal etiology was entertained clinically in only 14 (28%) of the patients. All 14 patients with diagnosed IMI were treated with mold-active antifungal agents (AF). Two

patients with not diagnosed IMI received a prophylactic treatment with a mold-active AF. However, in 40 (80%) patients IMI was the primary cause of death. Infected sites were lung 40 (80%), disseminated IMI 9 (18%), sinus 1 (2%). The major underlying conditions were: 12 (24%) patients after solid organ transplantation, followed by 11 (22%) patients with solid organ cancer, 7 (14%) patients with rheumatologic or immunological disorders receiving high dose corticosteroids, 6 (12%) patients with prolonged ICU stays, 6 HIV patients (12%), 5 (10%) patients hemato-oncological tumors, 3 (6%) with chronic lung disease. 31 (66%) patients were hospitalized on intensive care units (ICU) for at least one day. The median SAPS II score was 45 (range 8-79) and the median ICU stay was 11 days (1-53).
Conclusion: This survey found IMI to be frequent in patients with a wide range of underlying conditions. The high incidence of not clinically entertained IMI should enhance the clinician's awareness and suspicion of potentially fatal invasive mold infections. Further, our findings confirm the importance of autopsy as a tool for quality control in medical diagnostic and therapeutic activity.

P117

Leberversagen bei einer viszeralen Leishmaniose (VL) mit sekundärer hämophagozytischer Lymphohistiozytose

Fehr R., Jeker R., Reinhart W.H. (Chur)

Fallbeschreibung: Ein 40jähriger Patient wurde mit Schüttelfrost und Fieber seit ca. 2 Wochen hospitalisiert. Die Reiseanamnese ergab einen Indienaufenthalt im Jahr zuvor. Es bestand keine Immunsuppression; ein HIV-Test war negativ. Klinisch fiel ein Status febrilis und eine Hepatosplenomegalie, im Labor eine Panzytopenie sowie eine Erhöhung der Transaminasen, Cholestaseparameter und LDH auf. Das Ferritin war mit 12000 µg/l deutlich erhöht. Differentialdiagnostisch stand neben einem Lymphom eine tropische Infektionskrankheit im Vordergrund. Eine Malaria wurde in 3 Blutausstrichen nicht gefunden. Serologisch ergab sich einzig ein Hinweis auf eine akute EBV-Infektion mit 8222 RNA-Kopien/ml. Im Verlauf trat eine Leberinsuffizienz auf. Das Ferritin stieg auf 160000 µg/l. Serologisch und mittels positiver RNA im Serum konnte eine Leishmanieninfektion diagnostiziert werden. Im Knochenmark war eine Hämophagozytose ersichtlich. Unter hoch dosierten Steroiden, Etoposid sowie Ambisome kam es rasch zur klinischen Besserung und Normalisierung des Ferritins.
Diskussion: Für die hämophagozytische Lymphohistiozytose sind die Klinik mit rezidivierenden Fieberschüben und Hepatosplenomegalie sowie die Panzytopenie und Hyperferritinämie typisch. Als Auslöser sind in der Literatur sowohl akute EBV-Infektionen als auch eine VL beschrieben. In unserem Fall bestand ein Co-Infektion. Wir denken, dass die VL massgebend war, da erst die antiparasitäre Therapie den Durchbruch brachte. Serologisch ist bei unserem Patienten eine EBV-Primoinfektion möglich, eine Reaktivierung einer chronischen EBV-Infektion unter der Immunschwäche bei VL jedoch wahrscheinlicher. Bei Kindern wurde ein signifikanter Zusammenhang zwischen VL und EBV-Primoinfekt aufgezeigt. Diskutiert wird eine Abnahme der leishmaniziden Aktivität der infizierten Makrophagen durch eine Verstärkung der TH2 Immunantwort durch das Virus. Dieser Fall zeigt auf, dass bei einer Panzytopenie, Hepatosplenomegalie und einer Hyperferritinämie eine VL serologisch und mittels PCR von Serum, Knochenmark oder Leber gesucht werden muss, auch wenn man serologisch Hinweise für eine EBV-Infektion hat. Denn das Verpassen einer VL ist letal, die Therapie mit Ambisome hingegen relativ untoxisch und wirkungsvoll. Eine VL und Leberversagen wurde bisher nur in der pädiatrischen Literatur beschrieben.

P118

Invasive Aspergillosen bei Patienten ohne Granulozytopenie: Risiko und prognostische Faktoren

Kaiser P., Moll C., Frauchiger B., Rochat P., Thurnheer R., Krause M. (Münsterlingen, Frauenfeld)

Hauptrisikofaktor für die Invasion von Aspergillen ist das Fehlen von Phagozyten. Deshalb kommen Aspergillusinfektionen am häufigsten bei Leukämiepatienten vor, welche über längere Zeit in der Aplasie sind. Wir beobachteten in den vergangenen Jahren wiederholt Aspergillosen bei Patienten, welche keine Agranulozytose aufwiesen. Ihre Charakteristika und Risikofaktoren wurden retrospektiv zusammengestellt.
Resultate: Von 1998–2007 wurden bei 14 Patienten eine Aspergilleninfektion bioptisch oder autoptisch diagnostiziert. Patienten mit Aplasie oder mit nicht-invasiver Aspergillenkolonisation waren ausgeschlossen. Bei 7 Patienten fand sich eine auf ein Lungensegment beschränkte Aspergilleninfektion und bei 7 eine multilobäre Lungeninfektion mit/ohne Dissemination. Bei 2 der 7 Patienten mit lokalisierter Aspergillenpneumonie handelte es sich um einen Zufallsbefund post mortem, bei 5 Patienten erfolgte die Diagnose im Rahmen der Abklärung eines Lungenbefundes. Bei 2 dieser 5 Patienten war das Mass der Gewebsinvasion durch *Aspergillus spp.* unsicher. Vier der 5 Patienten wurden fungistatisch behandelt und bei 3 wurde eine Lungenteilsresektion durchgeführt. Alle hatten als Prädisposition eine vorbestehende Lungenpathologie (COPD, St. n. Tbc), jedoch erhielt keiner länger dauernd systemische Kortikosteroide oder andere Immunsuppressiva. Alle Patienten hatten einen günstigen Verlauf. Bei allen 7 Patienten mit multilobärer Pneumonie war eine hochdosierte Kortikosteroidtherapie über Wochen vorausgegangen. Bei 4 Patienten bestand als Grundleiden ein metastasierendes solides Karzinom mit Hirnmetastasen, bei 3 eine vaskulitische Erkrankung. Alle Patienten verstarben, wobei die Aspergilleninfektion wesentlich zum Ableben beitrug. Die Dissemination erfolgte bei 5 Patienten, es fanden sich Pilzhyphen in Hirn, Niere und Herz.
Schlussfolgerung: Lokalisierte Infektionen in der Lunge kommen vor allem bei vorbestehenden Lungenpathologien vor und haben bei Einsatz von Fungistatika und Chirurgie eine gute Prognose. Im Gegensatz dazu haben multilobäre Aspergilluspneumonien mit Dissemination eine sehr hohe Mortalität. Hauptrisikofaktor dafür sind hochdosierte Kortikosteroide über mehrere Wochen.

P119

Use of activated protein C in a patient with miliary tuberculosis and multiorgan failure

Ribaudo G., Nisslé S., Piso R.J., Paganoni R., Bassetti S. (Olten)

Objectives: To describe a case of miliary tuberculosis (MT) with multiorgan failure that was treated with recombinant human activated protein-C (rhAPC, Drotrecogin alpha activated). Although rhAPC is indicated for patients suffering from severe sepsis and septic shock with a high risk of death, to our knowledge, only one case of miliary tuberculosis treated with rhAPC has been described in the literature. This patient died despite treatment. We report the first case of a MT-patient successfully treated with rhAPC.
Methods: MT is a form of sepsis and refers to clinical disease resulting from the uncontrolled hematogenous dissemination of Mycobacterium tuberculosis. Sepsis due to tuberculosis is uncommon and often goes unrecognized by clinicians. With the advent of HIV, there is evidence that MT is becoming more prevalent. Despite effective therapies for less severe forms of tuberculosis, MT still carries an almost uniformly fatal prognosis if diagnosis is delayed. We describe a case of MT in a 36-year-old HIV positive woman admitted to hospital with increasing fatigue, weakness, fever and cough. M. tuberculosis was cultured from bronchoalveolar lavage fluid, urine and faeces. Chest radiograph in the course of hospitalisation demonstrated diffuse bilateral interstitial infiltrates. 5 days after starting empiric antimycobacterial therapy with rifampin, isoniazid, pyrazinamide and ethambuthol, the patient developed respiratory insufficiency, septic shock and disseminated intravascular coagulation, and had to be intubated and transferred to the intensive care unit. Here she was started on rhAPC treatment. Corticosteroids were also administered.
Results: All patient's severe clinical manifestation of sepsis improved markedly during or shortly after the treatment period on rhAPC, and after 8 days our patient was extubated and finally survived the severe sepsis.
Conclusion: Our case report supports the use for rhAPC in MT. Although it is impossible to prove that the patient's improvement was due to rhAPC alone, her clinical improvement was atypical for MT and corresponded temporally to the use of rhAPC. In placebo-controlled trials rhAPC demonstrated significant mortality benefit in patients with severe sepsis, but none of the trials included any patients with MT. There is evidence that MT shares with other bacterial infections some of the sepsis-pathways that are modulated by rhAPC. Therefore, there is also a scientific rationale for the use of rhAPC in MT.

P120

Streptococcus oralis-Meningitiden mit Fokus im Hals-Nasen-Ohrenbereich

Peternac D., Rochat Ph., Frauchiger B. (Frauenfeld)

Bakterielle Meningitiden mit S. oralis sind selten und wurden fast ausschliesslich nach zahnärztlichen Eingriffen und selten nach neurochirurgischen Interventionen (Einlage externe Ventrikeldrainage, Bandscheiben-Nukleolyse) beschrieben. Wir berichten über zwei Fälle mit primärem Fokus im HNO-Bereich.
Fall 1: Ein 30jähriger Patient litt seit drei Tagen an Halsschmerzen und entwickelte akut einsetzende, frontal betonte Kopfschmerzen. Klinisch bestand ein Meningismus. Die Leukozyten betrugen 12,1x10^9/l und das CRP 24 mg/l. Die Zellzahl im Liquor war 2667x10^6/l (98% Polynukleäre). Unter einer Behandlung mit Ceftriaxon und Dexamethason verbesserte sich der Zustand. In der Liquorkultur liess sich S. oralis nachweisen. Im Verlauf trat eine Liquorrhoe auf mit Nachweis von [beta]-2-Transferrin. Bereits mit 20 Jahren erkrankte der Patient an einer bakteriellen Meningitis mit damals nicht nachweisbarem Erreger. Durch eine zweite, hochauflösende Schädelcomputertomographie war ein 10x6 mm messender ossärer Defekt der rechten Lamina cribrosa mit intrakranieller Kommunikation darstellbar. Eine in der Kindheit berichtete passagere Rhinorrhoe dürfte damals bereits einer Liquorrhoe entsprochen haben. Nach 15-tägiger Hospitalisation mit residueller Gangataxie erfolgte eine erfolgreiche operative Dekkung des ossären Defektes.
Fall 2: Ein 61jähriger Patient wurde mit Meningismus und einer eitrigen Otorrhoe links zugewiesen. Das CRP war normal mit Leukozyten von 12,4x10^9/l. Im trüben Liquor fanden sich 20'171x10^6/l polynukleäre Zellen. Das Schädel-CT ergab eine Otitis media mit Mastoiditis links und in der Feinschichtung fand sich ein intrakranieller Durchbruch des lateralen Felsenbeines. Im Liquor waren keine Erreger nachweisbar, in den Blutkulturen wuchs S. oralis. Unter der Behandlung mit Ceftriaxon verbesserte sich die anfängliche Vigilanzstörung und das Fieber war rückläufig. Nach drei Tagen wurde eine Mastoidektomie mit Einlage einer Drainage durchgeführt.
Konklusion: S. oralis ist ein Keim der Mundflora und gehört zur Gruppe der Viridans-Streptokokken. Bisher wurden gemäß unserer Kenntnis noch keine S. oralis-Meningitiden ausgehend von einem Primärfokus im HNO-Bereich in den uns zugängigen Datenbanken publiziert. Neben den dafür bekannten Bakterien wie Pneumokokken, Meningokokken, H. influenzae, Listeria monocytogenes und verschiedenen Viridans-Streptokokken kann neu auch S. oralis als Erreger in Betracht gezogen werden.

P121

Granulomatous hepatitis after intravescical Calmette-Guérin bacillus treatment

Adami M., Marsteller I., Riglietti A., Mazzucchelli L., Cerny A., Bernasconi E. (Lugano, Locarno)

Local instillation of Calmette-Guérin bacillus (BCG) is an effective therapy for superficial bladder cancer and adverse reactions are uncommon. However, serious complications such as disseminated infection with sepsis, granulomatous hepatitis, pneumonitis or osteomyelitis, have been reported and should be considered in the differential diagnosis of a deteriorating patient after BCG treatment. We describe a 79 year-old man who presented at the emergency department with mental confusion, chills, fever, tachypnea, tachycardia, jaundice and abnormal liver function tests, eight hours after a first BCG intravescical instillation. Rapid clinical improvement was observed. Cefepime and Acetaminophen treatment was continued suspecting septicaemia. Blood and urine cultures were sterile, liver function tests remained abnormal. Four weeks later he presented again with fever, anorexia, jaundice and fatigue, as well as worsened liver function tests. Abdominal ultrasound revealed normal liver structure and narrow bile ducts, whereas splenomegaly was detected. Liver biopsy showed multiple non-caseating granulomas compatible with a BCG hepatitis, even if Ziehl-Neelsen stain didn't show alcohol-acid fast bacillus. Anti-mycobacterial treatment with Rifampin, Isoniazid and Ethambutol was started and continued for a total of 6 months, with complete clinical recovery and marked improvement of liver function tests. Neither the mechanism of action of BCG as an immunotherapeutic agent in cancer nor the mechanism of systemic infection is completely understood. In conclusion, we believe that the first episode represents an hypersensitivity reaction, whereas further clinical course and findings at liver biopsy strongly suggest secondary dissemination of BCG.

P122

Erythroblastopénie récidivante chez une patiente HIV positive

Calmy A., Wintsch J., Inoubli S., Mach-Pascual S., Verholen F., Lebeau O., Hirschel B., Beris P. (Genève)

Une patiente née en 1959, HIV + depuis 1986, sous traitement antirétroviral de darunavir/ritonavir, étravirine et enfuvirtide, a été hospitalisée en août 2007 pour fatigue extrême et dyspnée, sans notion de saignements. Status: absence de fièvre, d'ictère, de lésion cutanée ou de splénomégalie, petite adénopathie cervicale, pâleur. A l'entrée: Hb 34 g/l, réticulocytes 1,4%0, plaquettes 39 G/l, leucocytes 2,5 G/l (63% neutrophiles; 9% lymphocytes; 9% myélocytes). CRP, LDH, fonctions hépatique et rénale sont dans la norme. Saturation de la transferrine 108%, ferritine 440 microg/l, sTfR 0.4mg/l, B12 111 pmol/l, folates 5nmol/l, sérologie CMV IgM négatif, EBV négatif, parvovirus B19 (PV B19) IgG positif 1/64. Cytométrie de flux: population B polyclonale; CD4/CD8 1/13, CD4 36 /microl. HIVRNA <40 copies. Ponction de moëlle: érythroblastes absents sauf rares proérythroblastes de grande taille avec parfois cytoplasme vacuolé. La patiente a été transfusée puis mise sous B12 et folates. Au vu d'une virémie DNA PV B19 très élevée (9,94 log copies/ml), elle a reçu des immuno-globulines (Ig) polyclonales (dose totale de 2 g/kg). 15 jours plus tard, les réticulocytes augmentent à 222 G/l et les plaquettes à 136 G/l. Un traitement d'entretien d'Ig (0,4 g/kg 1 fois par mois) est donc instauré. On observe alors une récidive de l'anémie érythroblastopénique avec des taux de PV B19 qui continuent d'augmenter. Les doses des Ig sont doublées, permettant la diminution de la virémie PV B19, mais sans effet sur l'anémie (Hb 68g/l). Les CD4 restent très bas (22 cellules/microl) et ce malgré un excellent contrôle de la virémie HIV. En conclusion, chez un patient sévèrement immunosupprimé, une infection à PV B19 (ou une réactivation) est une complication connue qui se manifeste essentiellement par une érythroblastopénie. Des pancytopénies ont toutefois été décrites. La persistance de la lymphopénie sévère prédit la récidive de l'anémie une fois que l'effet des Ig à hautes doses s'épuise, comme c'est le cas chez cette patiente. L'administration de la dose complète d'Ig (2 g/kg/mois) nous paraît donc indiquée en absence d'option pour favoriser la reconstitution immune. Une alternative thérapeutique séduisante mais non documentée serait de lui transfuser un plasma riche en anticorps anti-PV B19.

P123

Aspergillose pulmonaire semi-invasive: challenge diagnostique?

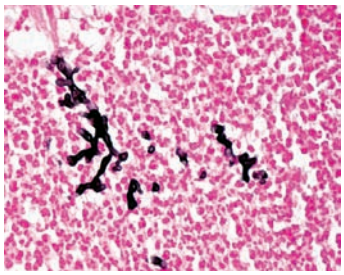
Carron P-N., Boillat N., Bille J. (Lausanne)

Introduction: L'aspergillose pulmonaire semi-invasive (APSI) est une entité méconnue, concernant classiquement des patients faiblement immunosupprimés. Un cas clinique récent permet d'en illustrer la présentation clinique, ainsi que la démarche diagnostique.
Cas clinique: Une patiente de 63 ans est hospitalisée en raison d'une décompensation diabétique, associée à des sudations nocturnes et des infiltrats pulmonaires, ayant motivé l'introduction d'amoxicilline – clavulanate (Fig. 1). Elle décrit également une perte pondérale de 6 kg en six mois, ainsi qu'une dyspnée et une toux productive. On note dans les antécédents un tabagisme actif (25 UPA), un ancien éthylisme et une pancréatite chronique avec un diabète secondaire. Le bilan initial révèle un syndrome inflammatoire modéré, une cholestase et des infiltrats pulmonaires nodulaires diffus. Un lavage broncho-alvéolaire, ainsi qu'une biopsie percutanée sous CT, révèlent des infiltrats inflammatoires aspécifiques. Les cultures et recherches microbiologiques par PCR, ainsi que le bilan immunologique sont négatifs. Le diagnostic est finalement posé lors d'une biopsie pulmonaire par thoracotomie, mettant en évidence de nombreuses colonies d'Aspergillus fumigatus (Fig. 2), associées à une invasion tissulaire et des foyers de nécroses. L'évolution est favorable sous traitement de voriconazole.
Discussion: Le diagnostique d'APSI est difficile et se base sur des critères cliniques (symptômes pulmonaires ou systémiques chroniques), radiologiques (cavité pulmonaire avec infiltrats paracavitaires) et microbiologiques (présence d'Aspergillus ou de précipitines aspergillaires). Dans 50% des cas, une biopsie pulmonaire chirurgicale est nécessaire pour confirmer le diagnostic, les biopsies trans-bronchiques ou percutanées étant de rendement médiocre. Le dosage des

antigènes galactomananes s'avère également le plus souvent négatif. La présence d'Aspergillus dans les prélèvements permet d'orienter le diagnostic et ne doit pas être considérée comme une simple colonisation.
Conclusions: L'APSI est vraisemblablement sous-diagnostiquée dans la population hospitalière helvétique. Les prévalences élevées de corticothérapie, de diabète, de bronchopneumopathie obstructive ou d'éthylisme chronique constituent en effet des facteurs de risques notables. Elle devrait être évoquée devant tout patient faiblement immunosupprimé, présentant des symptômes pulmonaires ou systémiques chroniques, avec des infiltrats pulmonaires cavitaires.

Fig. 1
Infiltrats pulmonaire CT

Fig. 2
Aspergillus – coloration argentique



P124

Six patients with herpes simplex type 2 central nervous system infection

Rohacek M., Rossi M., Ziegler F., Hodel T., Bloetzer I., Elsasser S., Henzen C. (Luzern)

Case report: We report six patients with a herpes simplex type 2 (HSV-2) central nervous system (CNS) infection seen within one year in our clinic. One 80 year old patient had chronic lymphatic leukaemia, the other patients were immunocompetent, HIV negative and were between 20 and 45 years old. One patient had a history of sexual transmitted disease, but no patient had a history of genital herpes. Two of them presented with meningoencephalitis including fever, stupor and epileptic seizures, one of whom developped brain edema and had to be intubated. Two patients presented with a first episode of an aseptic meningitis, two patients had a recurrence. All patients showed monocuclear pleocytosis ranging from 48 to 592 cells/ul and amplification of HSV-2 DNA in the cerebrospinal fluid (CSF). The number of cells per ul CSF or the blood level of C-reactive protein (CRP) did not correlate with symptom severity. All patients were seropositive for HSV-IgG, but only one showed positive IgM. After treatment with Acyclovir, all patients recovered well without neurological deficites.
Comment: CNS-infections by HSV-2 are rare. There are only a few data concerning epidemiology. The annual incidence rate of HSV-2 CNS disease is described to be 0.26 per 100,000. In one study of 49 patients with HSV-2 DNA in the CSF, 43 (88%) had meningitis of whom eight (19%) had recurring lymphocytic meningitis. Only six patients (12%) had encephalitis. HSV-2 is not a common cause for encephalitis in contrast to HSV-1, varizella zoster virus (VZV), tick-borne encephalitis virus or enterovirus.
Conclusion: HSV-2 does not only cause aseptic meningitis, but can also cause severe encephalitis. The majority of our patients were negative for HSV-IgM, so reactivation of the virus is probable to be the cause of their disease.

P125

Clinical impact of renal function-dependent variability of imipenem and cefepime blood levels in febrile neutropenic patients

Lamoth F., Pascual A., Vora S., Bolay S., Calandra T., Marchetti O. (Lausanne)

Background: Imipenem and cefepime are standard therapies in febrile neutropenia. Renal clearance is the major elimination pathway of these antibacterial agents. An important intra- and inter-individual variability of drugs blood levels has been reported. Low or high drug blood levels may result in decreased efficacy or toxicity, respectively. Although therapy failure or adverse events occur frequently in febrile neutropenic patients, their causes remain often unknown.
Objective: To evaluate the clinical impact of renal function-dependent low and high trough blood levels of imipenem and cefepime in febrile neutropenic patients.
Methods: Eighty-one therapy courses were studied retrospectively: 51 imipenem, 30 cefepime. Trough blood levels were interpreted as i) low: <MIC or <MIC90 of the most common bacterial pathogens (1 mg/L for imipenem, 2 mg/L for cefepime) or ii) high: >15 mg/L. The clinical significance of low or high blood levels was evaluated by clinical response of infection to therapy or presence of clinical signs of toxicity, respectively.
Results: An important variability of drugs blood levels was observed. 22/51 (43%) imipenem trough levels were interpreted as low. In 4/51 cases (8%) lack of response of infection to therapy was attributed to low drug levels and all responded to dose adjustment. 12/30 (40%) cefepime trough levels were >15 mg/l: in 6/30 cases (20%) high levels were associated with neurological toxicity and all completely recovered after dose decrease or therapy discontinuation. Imipenem underdosing with lack of response (3/4, 75%) and cefepime overdosing with neurotoxicity (6/6, 100%) were mainly observed in patients with creatinine clearance > and <70 ml/min, respectively, whereas drugs dosing schedules were similar in patients with normal or impaired renal function.
Conclusions: Low blood levels of imipenem and high levels of cefepime are observed in febrile neutropenic patients with normal and impaired renal function, respectively. Monitoring of blood levels of beta-lactam antibiotics with individualized dose adjustments may improve efficacy and safety of antibacterial therapy in febrile neutropenia.

Figure 1
Imipenem blood levels and renal function

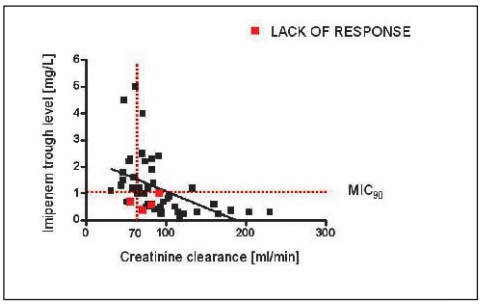
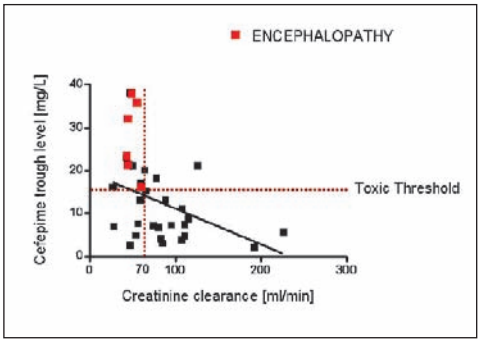


Figure 2
Cefepime blood levels and renal function



P126

Pylephlebitis associated with choledocholithiasis

Conzett Th., Graber P., Glauser Ph., Zimmerli W. (Liestal)

Background: Pylephlebitis (septic thrombophlebitis of the portal vein) is a rare, life-threatening complication of intraabdominal infection.
Case report: A 73-year-old man was hospitalized in November 2007 because of abdominal pain in the right upper quadrant, chills, nausea and anorexia. Treatment with ciprofloxacin was initiated by the general practicioner because of suspected pyelonephritis. On admission, the patient was afebrile, blood pressure and pulse rate were normal. Physical examination revealed a tender right subcostal region. Laboratory tests showed leucocytosis of $20.5x10^9$/L (neutrophils 90%), thrombocytosis of $423x10^9$/L and a C-reactive protein of 17 mg/L. Elevated alkaline phoshatase (147 U/L), gamma-GT (1914 U/L), amylase (1604 U/L), lipase (6775 U/L), AST (780 U/L) and ALT (407 U/L) were compatible with acute biliary obstruction. Blood cultures were negative. Contrast-enhanced CT-scan showed a prepapillary bile duct stone, thrombosis of the right portal venous branch and a hypointense zone in the right liver lobe. Treatment with piperacillin/tazobactam was started. A follow-up CT-scan revealed spontaneous clearance of the concrement; however, an increased hypodense area, suggested liver abscess formation. CT-guided drainage produced 500 ml pus growing monoculture of *Bacteroides fragilis*. Long-term treatment with oral metronidazole was initiated, and the patient gradually recovered.
Discussion: Pylephlebitis is an uncommon complication of suppurative infection (mainly diverticulits and appendicitis) in the portal drainage area with a high mortality (>30%). Liver abscesses are a frequent complication. In the literature, only one case has been associated with cholelithiasis. Contrast-enhanced CT-scan allows rapid diagnosis. Empiric broad spectrum antibiotics are needed because polymicrobial bacteremia is frequent. There are no data on a benefit of anticoagulation.
Conclusions: Pylephlebitis should be suspected in patients with severe intraabdominal infection. Raised clinical awareness, adequate radiological imaging, and a thorough evaluation and treatment of a primary or secondary bacterial focus are crucial.

P127

Documentation of low voriconazole blood levels followed by dose adjustment in patients with invasive fungal infections not responding to therapy

Pascual A. A., Bolay S., Marchetti O. (Lausanne)

Background: Voriconazole (VRC) is a new standard for treatment of invasive fungal infections (IFI). Inter-individual variability of VRC blood levels has been described. Recent reports suggest that low blood levels might be associated with failure of VRC therapy (Rx).
Objective: To assess the utility of documentation of low VRC blood levels followed by dose adjustment in patients (Pts) not responding to Rx.
Methods: Retrospective analysis of Pts receiving VRC for proven or probable IFI (EORTC-BAMSG) over 2004–2006. Definitions: success = partial or complete resolution, failure = persistent or progressing IFI. VRC blood levels measured by HPLC. Failure in with a VRC trough level ≤1 mg/L (MIC90 of the most fungal pathogens) was the trigger for dose adjustment.
Results: 37 Pts (all caucasians) were studied. Median age: 60 (23 to 78). 68% had aspergillosis, 22% candidiasis and 10% other IFI. Median VRC dose: 8 mg/kg/d for a median duration of 50 days. Among 6 Pts with VRC failure and trough levels ≤1 mg/L, 4 had proven (MIC of VRC <0.5 mg/L) and 1 probable aspergillosis; 1 had probable candidiasis. VRC dose was increased in the 6 cases: median follow-up VRC trough level was 2.1 mg/L (0.8 to 3.1). All Pts had partial or complete response. 2 patients with VRC failure and trough levels >1 mg/L responded to salvage Rx.
Conclusions: Documentation of low VRC blood levels followed by dose increase may improve outcome in Pts with invasive fungal infections not responding to Rx.

P128

Efficacy of patient versus healthcare provider based interventions in increase screening rates, knowledge and awareness of colorectal cancer screening: a systematic review

Dash C., Guessous I. (Atlanta, Lausanne)

Background: Interventions to increase knowledge of and awareness about colorectal cancer (CRC) screening target patients or healthcare providers, but it is unknown which approach is more effective. The goal of our review was to identify and assess interventions aimed at increasing awareness about CRC screening among average risk patients and healthcare providers and to compare their efficacy.
Methods: Studies were identified by searching Medline between 1995 and June, 2007. Three comprehensive search themes were developed and combined using the Boolean operator "and". All intervention studies that had a component for increasing CRC awareness in either patients or providers or both were selected for review.
Results: Fifty-two studies met the eligibility criteria. The majority (66%) involved use of one or more multimedia components to provide education on CRC risk factors and screening options. Interventions among the 14 studies that targeted healthcare providers were provider/clinician education (71%), provision of screening tool kits (29%), questionnaires/reminders to identify patients that require screening (21%), help with patient notification of test results (14%), and organization level CRC screening quality improvement programs (14%). Of the studies that reported screening outcomes, 73% (29/40) reported a significant change in the outcome post-intervention. Components of awareness intervention directed towards screening recipients or patients that were found to be most effective were patient navigators, in-person counseling by nurse/provider educators, and targeted/tailored multimedia educational materials. Successful components of the healthcare provider based interventions were educational and other initiatives targeted to individual providers rather than organizations. We found no evidence that studies targeting providers were more likely to report significant effect of the intervention on the screening outcome as compared to those targeting patients. We also did not find enough evidence to conclude that studies targeting providers were more likely to report significant effect of the intervention on attitude/knowledge outcomes compared to those targeting patients
Conclusions: Most interventions are effective at increase CRC screening rates. We did not find any statistically significant difference between healthcare provider and patient based interventions in increasing screening rates and knowledge.

P129

Use of transdermal opioids in cancer patients referred to a mobile palliative care team

Escher M., Besson M., Piguet V. (Genève)

Background: Although it is recommended to use short acting opioids to rapidly relieve uncontrolled pain, slow-released morphine can also be used effectively. Transdermal systems are slow-released devices which prolong the apparent half-lives of opioids even more. The aim of this study was to determine if cancer patients receiving transdermal opioids (TO), and referred to our palliative care team for uncontrolled pain could be maintained on TO.
Methods: Retrospective chart review of the cancer patients hospitalised in the Geneva University Hospitals between January 1st, 2006 and July 31st, 2007, and receiving transdermal buprenorphine or fentanyl when first assessed.
Results: Among 158 patients, 29 patients (18.3%) were included. Twenty-one were on transdermal fentanyl. Mean age was 60.5 +/- 14.6 years. Pain was mainly related to bone metastasis (n = 11) and head and neck cancer (n = 6). Eight patients had abdominal pain due to peritoneal carcinomatosis or primary cancer. TO were continued in 23 patients (79.3%). Reasons to stop TO were severe pain (n = 3), lack of efficacy of TO (n = 2), and simplification of treatment (n = 1). Pain tended to be more severe in patients whose TO was stopped (mean VAS 90 vs 72 mm; p = 0.09) There was no difference in the time needed to relieve pain.
Conclusions: Adequate pain relief can be obtained with transdermal opioids despite their slow-released formulation. Appropriate assessment of the patient's situation is the key factor for individualised treatment.

P130

Psychological adjustment in hospitalised cancer patients

Cedraschi C., Luthy C., Konrad-Mugnier B., Arigoni F., Rapiti E., Allaz A.F. (Geneva)

Background: Cancer patients experience distress and develop a variety of cognitive and emotional reactions in their attempts to adjust to disease and illness. An active or proactive adjustment may be associated with less distress.
Objective: To investigate the association between mental adjustment and the psychological impact of the disease in terms of anxiety and distress in a supportive care setting.
Methods: 83 consecutive patients hospitalized in a supportive care unit responded to a questionnaire including psychological dimensions investigated by the Hospital Anxiety and Depression Scale (HADS), the Distress Thermometer (DT) a graphic scale rated from 0–10, and the Mental Adjustment to Cancer index (MAC). Socio-demographic and clinical characteristics were also recorded, along with functional aspects (Performance Status), and the Physician Global Clinical Impression (PGCI) a numerical scale rated from 0–10 assessing the estimated survival prognosis at the admission.
Results: 67% of the patients were men; mean age was 65 years (SD = 14). A wide range of cancer diagnoses were represented. Median time since diagnosis was 1.8 years (range = 0.1–12.5 years). A wide range of cancer diagnoses were represented: head (7%) and neck (7%), gastro-intestinal (22%), lung (28%), breast (9%), gynecological (7%), genito-urinary tract (9%) hematological (4%) and other locations (7%); 23% had primary local diseases, 42% had local recurrences, and 35% had metastatic diseases. Anxiety and depression rating scores were moderate to high (mean HADS: 10.5 ± 0.5 and 10 ± 0.5, respectively; mean DT score: 4.7 ± 0.2). The results of linear correlation tests showed a statistically strong and inverse association between the dimension referring to fighting spirit in the MAC and anxiety and depression as measured by the HADS ($p < 0.001$), by the DT ($p < 0.001$), and by specific subscales of the MAC ($p < 0.001$). Fighting spirit was also significantly associated with a better evaluation of patient's performance status by the physician ($p < 0.01$) as well as with a better PGCI ($p < 0.01$). On the contrary, hopelessness/ helplessness was associated, although not significantly, with a worse PGCI.
Conclusions: Cancer patients hospitalized in a supportive care unit experienced a high psychological impact of the disease both in terms of anxiety and depression. Mental adjustment seemed to play a buffering role insofar as mental adjustment strategies allowing for a sense of control on the disease was related to a better psychological well-being. Those patients who endorsed such an adjustment strategy were also those who gave rise to better global clinical prognostic evaluations and performance status as evaluated by the physicians.

P131

Ergebnisse eines Praxiserfahrungsberichtes zum Management der chemotherapieinduzierten Anämie mit Darbepoetin alpha in der Schweiz

Piguet D. (Biel)

Hintergrund: Die Anämie ist eine häufige Begleiterscheinung bei Patienten mit Krebs. Verursacht wird diese häufig durch myelotoxische Effekte der Chemotherapie. Bei symptomatischen Patienten mit einem Hb zwischen 9–11g/dl wird der Einsatz von ESAs (erythropoietic stimulating agents) empfohlen. Der Einsatz von ESAs hat zwei Zielsetzungen: Verbesserung der Lebensqualität sowie Verhinderung der Transfusion.
Methoden: In einem offenen nicht-randomisierten multizentrischen Praxiserfahrungsbericht wurden zwischen November 2005 und Dezember 2006 238 Patienten unter Chemotherapie aus 38 Zentren eingeschlossen, bei denen der behandelnde Arzt die Indikation zur Therapie mit ESA gestellt hatte. Ziel war die Untersuchung der Effizienz der Transfusionsverhinderung durch Darbepoetin alpha unter Praxisbedingungen.
Resultate: 19% der eingeschlossenen Patienten hatten Tumore der Lunge, 12% Brustkrebs, jeweils 7% Multiples Myelom, Non-Hodgkin Lymphom und Prostatakarzinom. Die eingesetzten Chemotherapien waren sehr heterogen. 78% der Behandlungen wurden ohne Transfusion durchgeführt. Bei 37% der Patienten wurde die Therapie mit ESA bei einem Hb-Wert um 10 g/dl initiiert. Bei 32% der Patienten lag der Ausgangswert vor Therapiebeginn unter 10 g/dl. Die Chance nicht zu

transfundieren korreliert mit der Höhe des Ausgangswerts des Hb. Beträgt diese bei einem Ausgangswert von 11 g/dl noch rund 85%, sind es bei 8 g/dl nur noch 44%. Umgekehrt proportional steigt der Bedarf an transfundierten Erythrozyten-Konzentraten. Bei Patienten, welche keine Transfusion benötigten, wurde der höchste Hb-Anstieg auf die erste Gabe ESA bei einem Ausgangswert von 9 g/dl registriert (0,8 g/dl). Der Appliktionsrhythmus liegt im Schnitt zwischen 3–4 Wochen, variiert jedoch stark. Die Zufriedenheit mit der Therapie ist gut (88% zufrieden bzw. sehr zufrieden). Ein klarer Zusammenhang zwischen Malignom oder Chemotherapie und der Chance nicht zu transfundieren konnte nicht etabliert werden.
Schlussfolgerung: Die Analyse der dokumentierten Fälle deckt sich mit den bisherigen Erkenntnissen aus der Therapie der Anämie mit ESA bei Patienten mit Krebs. Der Therapieentscheid wird tendenziell spät gefällt, knapp entsprechend den aktuellen EORTC-Richtlinien. In diesem Praxiserfahrungsbericht war die Chance grösser, die Therapie ohne Transfusion durchzuführen, wenn der Entscheid zum ESA-Einsatz bei einem höheren Hb-Ausgangswert gefällt wurde.
Mit Unterstützung von Amgen Switzerland AG ermöglicht.

P132

Therapie der multizentrischen Castleman Krankheit bei HIV-positiver Patientin: Fördert Rituximab die Progredienz des Kaposi-Sarkoms?

Buchkremer J., Küng M., Chuard C., Betticher D. (Freiburg)

Die multizentrische, HIV -und HHV-8 (humanes Herpesvirus 8) – assozierte Form des M. Castleman ist eine seltene lymphoproliferative Erkrankung mit schlechter Prognose. Aktuell existiert keine Standard-Therapie; die systemische Chemotherapie kombiniert mit dem CD20-Antikörper Rituximab wurde in Studien als effizient beschrieben. Fallberichte weisen darauf hin, dass die Rituximab-Therapie das Risiko erhöhen könnte, ein Kaposi-Sarkom zu entwickeln.
Eine 51jährige, aus dem Kongo stammende, HIV-positive Patientin (CDC-Stadium C3, Erstdiagnose 02/2007) wurde mit Fieber, generalisierter Lymphadenopathie, Splenomegalie sowie sehr schlechtem Allgemeinzustand (PS 4) und folgenden Parametern hospitalisiert: CRP 219 mg/l; Alb 21 g/l, LDH 494 U/l. Die axilläre Lymphknotenbiopsie zeigte regressiv veränderte, z.T. hyalinisierte Keimzentren sowie eine vaskuläre Hyperplasie mit zahlreichen, reifen Plasmozyten, vereinbar mit M. Castelman (gemischter Typ hyalin-vaskulär und plasmozytär), HHV-8 assoziert. Bei einer tiefen CD4-Zahl (177 Zellen/mm^3) und hohem viral load (379 000 copies/ml) wurde eine HAART (Tenofir, Lamivudin und Efavirenz) eingeleitet. Unter Chemotherapie mit CHOP (Cyclophosphamid, Doxorubicin, Vincristin und Prednison) kombiniert mit dem CD20-Antikörper Rituximab in 3 wöchigen Abständen konnte eine rasche Verbesserung des Allgemeinzustandes, des inflammatorischen Syndroms und eine sehr gute partielle Remission der Lymphadenopathien und der Splenomegalie festgestellt werden. Beim 3. Chemotherapiezyklus wurden kutane Läsionen festgestellt und bioptisch als Kaposi Sarkome bestätigt. Die bisherige Chemotherapie wurde daraufhin durch liposomales Doxorubicin ersetzt und die antivirale Therapie geändert (Efavirenz durch Saquinavir und Ritonavir ersetzt), was nach 3 Zyklen zur Regredienz der Kaposi-Sarkome führte. Unter Wiederaufnahme der Rituximab-Therapie trotz Weiterführung des liposomalen Doxorubicins kam es zur erneuten Progredienz der Kaposi-Sarkome. Der Verlauf bei dieser HIV-positiven Patientin zeigt, dass Rituximab in der Therapie des multizentrischen M. Castleman hochaktiv ist. Hingegen wird der Verdacht erhärtet, dass Rituximab die Progredienz des Kaposi-Sarkoms nicht aufzuhalten vermochte, ja möglicherweise sogar förderte.

P133

Long-term survival of a patient with advanced duodenal solid cancer treated with neoadjuvant chemotherapy followed by surgical resection: a case report

Roggero E., Palumbo A., Pelloni A., Huber O., Bigger P., Pedrazzini A. (Locarno, Geneva)

Neoplasia of the small bowel is rare, accounting in the literature and in our hospital series in the last 5 years for about 2–3% of all gastrointestinal neoplasms. Diagnosis and treatment of these diseases are major challenges and the exact modalities to cure these neoplasms are still unknown. We present a case report of a patient with a long-term survival of a locally advanced duodenal cancer treated with chemotherapy followed by radical surgery. In April 2001, a 41-year-old man suffering from vomiting and sensation of nausea and high abdominal obstruction attended our surgical-oncological department. A solid mass of the third part of the duodenum was found with direct compression of the pancreas and mesenteric vessels as confirmed by CT and MRI. Biopsies of the duodenal obstructive mass (8 cm x 8 cm) were performed and histological features revealed an intermediate differentiated adenocarcinoma. Due to the extension of the carcinoma, after multidisciplinary discussion, we decided to postpone surgery after a neoadjuvant chemotherapy. The patient was treated with irinotecan (150 mg/m^2) and gemcitabine (1000 mg/m^2) each lasting two weeks from June 2001 to March 2002. After ten months a CT diagnosis showed a wide partial regression of the duodenal mass (3 cm x 2 cm). The patient then underwent a Wipple resection. A histological examination confirmed an adenocarcinoma of the duodenum infiltrating the intestinal wall with mucosal ulceration and no tumoral invasion of the 24 examinated lymph nodes (stage T3 N0 M0). The postoperative course was complicated by a relaxation of the pancreatico-jejunal anastomoses with a consequent hemorrhage that necessitated an intervention of a total pancreatectomy and splenectomy. Subsequently, thirty-five days after the first surgical intervention the patient developed a cataclysmic hemorrhage with hypovolemic shock due to perforation of the mesenteric artery and relaxation of the gastro-enterostomy anastomosis resulting in a new laparatomy and surgical management. No other chemotherapy was done. Eighty-eight months after diagnosis the patient is free of duodenal neoplasia. The history of this case raises at least two points of discussion. The first regards the schedule and duration of the treatment. In our case a long (ten months) neoadjuvant chemotherapy treatment (with gemcitabine and irinotecan) seems to be associated with extended tumor shrinkage and complete resection of a locally advanced solid adenocarcinoma of the duodenum. The second regards complications of treatments. Major life threatening complications were observed: the relaxations of the anastomoses and the hemorrhages. In conclusion, because the rarity of this disease the best therapeutic approach is not defined, however, the use of chemotherapy before surgery should be discussed in these diseases.

P134

A new, automated, four-colour interphase FISH approach for the simultaneous detection of specific aneuploidies of diagnostic and prognostic significance in high hyperdiploid ALL

Talamo Blandin A., Muehlematter D., Bougeon S., Gogniat C., Porter S., Beyer V., Parlier V., Beckmann J. S., van Melle G., Jotterand M. (Lausanne)

In hyperdiploid acute lymphoblastic leukaemia (ALL), the simultaneous occurrence of specific aneuploidies confers a more favourable outcome than hyperdiploidy alone. Interphase (I) FISH complements conventional cytogenetics (CC) through its sensitivity and ability to detect chromosome aberrations in non-dividing cells. To overcome the limits of manual I-FISH, we developed an automated four-colour I-FISH approach and assessed its ability to detect concurrent aneuploidies in ALL. I-FISH was performed using centromeric probes for chromosomes 4, 6, 10 and 17. Parameters established for automatic nucleus selection and signal detection were evaluated (3 controls). Cut-off values were determined (10 controls, 1000 nuclei/case). Combinations of aneuploidies were considered relevant when each aneuploidy was individually significant. Results obtained in 10 ALL patients (1500 nuclei/patient) were compared with those by CC. Various combinations of aneuploidies were identified. All clones detected by CC were observed by I-FISH. I-FISH revealed numerous additional abnormal clones, ranging between 0.1% and 31.6%, based on the large number of nuclei evaluated. Four-colour automated I-FISH permits the identification of concurrent aneuploidies of prognostic significance in hyperdiploid ALL. Large numbers of cells can be analysed rapidly by this method. Owing to its high sensitivity, the method provides a powerful tool for the detection of small abnormal clones at diagnosis and during follow up. Compared to CC, it generates a more detailed cytogenetic picture, the biological and clinical significance of which merits further evaluation. Once optimised for a given set of probes, the system can be easily adapted for other probe combinations.

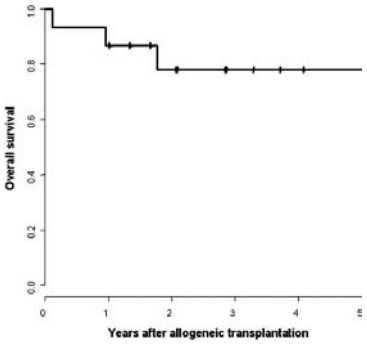
P135

Allogeneic HSCT for chronic lymphocytic leukemia: a single center experience

Stern M., Arber C., Buser A., Halter J., Heim D., Favre G., Gratwohl A. (Basel, Liestal)

Current chemotherapy regimens for CLL incorporating nucleoside analogues and monoclonal antibodies have high response rates. However, CLL remains incurable by standard chemotherapy. While allogeneic transplantation is potentially curative, high rates of early transplant related mortality using myeloablative regimens have precluded its widespread use in CLL. We report the outcome of patients treated with allogeneic transplantation at our institution since 2002. Sixteen patients (7 female/9 male; median age 52 years) received allogeneic HSCT between 2002 and 2007. Donors were HLA-identical siblings in 14 cases, matched unrelated donors in the remaining two. Indications for allogeneic transplantation were insufficient response to treatment with nucleoside analogues (fludarabine or cladribine) in 8 patients, del17p in 3 patients, and other in the remaining 5 patients. The conditioning regimen was Fludarabine/2 Gy TBI in six patients, BEAM/Fludarabine/2Gy TBI in seven patients, and Fludarabine/Cyclophosphamide in three patients. All transplants were T-cell replete, GvHD prophylaxis consisted of cyclosporine/methotrexate or cyclosporine/mycophenolate. Only one of the sixteen patients was in complete remission at the time of transplant. Thirteen patients were alive at last follow-up, three had died (two from infection, one from graft rejection). Of the patients alive, 11 are in complete remission, two have never achieved CR and are alive with progressive disease. Kaplan-Meier estimated overall survival at 5 years was 78% (Figure 1). Cumulative incidence of grade II or higher acute GvHD was 44%. Chronic GvHD was seen in 6/12 patients evaluable and was extensive in all patients. Allogeneic HSCT induced complete remission in the majority of cases in this population of patients with high-risk CLL. The survival rate compares favourably with literature data and with outcome of non-transplant treatment modalities. Allogeneic should be considered early in patients with high risk CLL.

Figure 1



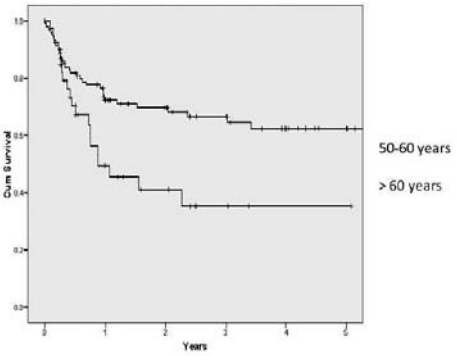
P136

Outcome of allogeneic stem cell transplantation in elderly patients with myeloid leukemias

Passweg J.R., Schanz U., Chalandon Y., Stussi G., Heim D., Halter J., Helg C., Tichelli A., Gratwohl A. (Genève, Zuerich, Basel)

The role of allogeneic hematopoietic stem cell transplantation (HSCT) in the treatment of patients with myeloid leukemia is not clear. This is particularly relevant in the elderly population given treatment related mortality risks. Reporting of all transplants is a legal requirement in Switzerland, and the STABMT (Swisstransplant Group for Blood and Marrow Transplantation) maintains a registry since 1997. We report here outcome data on 151 patients over the age of 50 having received an allogeneic transplant since 1997. Transplants were for acute myeloid leukemia (73, 40 in CR1, 33 with more advanced disease) chronic myeloid leukemia (24) or myelodysplastic/myeloproliferative syndromes (54). 111 patients were 50–60 years old, 40 were over 60. Median age was 56 years (range 50–70). Median follow-up of surviving patients was 25 months. Donors were siblings (112) unrelated (35) and others (4). Stem cell source was marrow in 13 and peripheral blood in the remainder. Patients above 60 were more frequently transplanted after 2001, were less likely to be transplanted for CML but donor type did not differ between patients 50–60 years of age and patients over 60. Overall survival at 5 years was 62 +/- 11% in patients 50–60 years old and 35 +/- 19% in patients over 60 (p = 0.007) (see figure). Treatment related mortality, defined as non relapse mortality was 17 +/- 8% in patients 50–60 years old and 31 +/- 26% in patients over 60 (p = 0.6). In multivariate analysis adjusting for age, disease and disease stage, year of transplant and donor type the only factors associated with increased risks of death were age >60 (RR: 2.1 p = 0.02) and advanced leukemia (RR 2.1, p = 0.07). Of note, there were no differences in outcome when unrelated (RR: 0.88, p = 0.7) were compared to sibling donors.
In conclusion: older patients undergoing allogeneic HSCT for myeloid leukemia may present with interesting long term outcome data. Comparison to other treatment modalities is needed, a randomized clinical trial comparing allogeneic HSCT to conventional chemotherapy is planned.

Fig. 1



P137

Use of a comprehensive national database as a quality control instrument

Passweg J.R., Bargetzi M., Halter J., Leoncini L., Leibundgut K., Pabst T., Chalandon Y., Duchosal M.A., Hess U., Seger R., Schanz U., Gratwohl A. (Genève, Aarau, Basel, Bellinzona, Bern, Lausanne, St.Gallen, Zuerich)

The goal of JACIE is quality improvement in all aspects of hematopoietic stem cell transplantation (HSCT). Reporting of all transplants and regular analysis of outcome is integral part of a quality management system. Few analyses have been done to assess the impact of a comprehensive HSCT data capture system on a national level and to use data comparison as a quality control tool. We made use of the legal requirement that all 9 HSCT teams in Switzerland, 1 allogeneic, 3 combined allogeneic-autologous and 5 autologous HSCT teams, do adhere to JACIE guidelines and do report all transplants to the STABMT (Swisstransplant Group for Blood and Marrow Transplantation) registry. From 1997–2006, 3868 HSCT, 29.4% allogeneic, 70.6% autologous were performed for 2987 patients, 60% male, 40% female, median age 46 (0–76.years). Main indications were leukemia (767 allo, 220 auto), lymphoproliferative disorders (138 allo, 1508 auto), solid tumors (8 allo, 333 auto) and non malignant disorders (92 allo, 10 auto). As of December 2007, 1899 patients (64%) were alive, 1079 (36%) had died, 249 (8.4%) from transplant related mortality (TRM) or 830 (27.9%) from disease progression. This corresponds to a survival probability of 50 +/- 3% in recipients of autologous HSCT and 57+/- 4% in recipients of allogeneic HSCT at 5 years whilst TRM probabilities were 7 +/- 2% and 20 +/- 3% respectively. Each team was assessed for survival and TRM data for each disease category and transplant type and data were compared with outcomes of all other teams combined. Data were adjusted in a multivariate regression model for the impact of transplant center adjusting for important factors associated with outcome, e.g. disease, disease stage, age, and histocompatibility. Separate models were constructed for allogeneic and autologous HSCT. There were no significant differences among teams in overall survival of allogeneic and autologous HSCT. There was a significant difference in models of

TRM due to 3 events in a small center for autologous HSCT but no center difference in TRM for allogeneic HSCT. Reasons for this outlier are being evaluated with the respective teams. These data show that a consistently high quality may be achieved in data monitoring within a country by a comprehensive database. Deviations are recognized rapidly and discussed with the respective teams. Such regular comparisons within the professional HSCT organizations may serve as a model for quality assurance.

P138

Physical but not mental health is inferior in very long term survivors after HSC compared to their respective donors: a pair analysis

Rovó A., Daikeler T., Stern M., Halter J., Studt J.D., Buser A., Heim D., Rischewski J., Medinger M., Tyndall A., Gratwohl A., Tichelli A. (Basel)

With the improvement of prognosis, health status and functional well being of long term survivors after HSCT become an important issue. We performed a prospective study on 44 long-term survivors and their respective sibling donors at a median of 17.5 years (range 11–26) after HSCT. The median age of the recipients and donors at time of the study was 44.3 (24–63) and 43.4 years (22–61) respectively. Both recipients and donors were seen on the same day for evaluation with the short form-36® (SF-36) Health Survey, which provides a generic health status measurement through 36 items assessing 8 concepts of health. Three of the items measure physical health (PF, RP, BP), two measure both physical and mental health (GH, VT), and three measure mental health (SF, RE, MH). In addition there are two summary scores for physical (PCS) and mental (MSC) health. For statistical analysis norm-based scoring (NBS) was used, where 50 is the mean score, and 10 the standard deviation of a defined general population. Paired analysis between donors and recipients were performed for detecting differences between donors and recipients. All scored items of recipients as well as of the donors were within the range of one standard deviation of the norm-based population. All scores concerning physical well being except one, (RP), were statistically lower in the recipients than in their donors. In contrast, there was no difference in scores concerning mental well being. This is confirmed by the summary measurements of physical health (PCS) with 52,8 in the recipients and 57,1 in the donors ($p = 0.001$) and mental health (MCS) with 50,8 versus 52,9 ($p = 0.831$). Physical health (PCS) was lowest in patients with severe chronic GvHD compared to their donors (47,2 versus 57,2) ($p = 0.05$), age older than 25 years at HSCT 50,7 versus 56,2 ($p = 0.024$), older than 42 years at the last control 52,2 versus 55,63 ($p = 0.05$) and for female patients 51,8 versus 57,7 ($p = 0.024$). None of the factors had a statistical impact on mental heath status (MCS, $P > 0.05$). In summary, quality of life of long term survivors after HSCT measured with the SF-36 questionnaire is still within the normal variation of the general population. However, when compared to the respective donors, the physical health status is significantly compromised in the recipients. Severe GvHD, older age at HSCT and at the time of filling out the questionnaire and female gender are associated with an inferior physical health status.

Table 1

Items	Label	Donor Mean	Recipient Mean	p value
Items describing physical health				
- Physical functioning	PF	54.7	50.9	.001
- Role limitations due to physical health	RP	54.6	52.3	.213
- Bodily Pain	BP	53.2	54.9	.042
Items describing general health (physical and mental)				
- General health perception	GH	57.0	50.7	.001
- Vitality	VT	55.4	52.3	.039
Items describing mental health				
- Social functioning	SF	54.0	51.2	.324
- Role limitations due to emotional problems	RE	53.9	51.0	.285
- Mental health	MH	52.7	50.9	.638
Global tests				
- Physical Component Summary	PCS	57.1	52.8	.001
- Mental Component Summary	MCS	52.9	50.8	.831

P139

Tumour incidence in donors of haematopoietic stem cells for their HLA identical siblings

Jeger A., Favre G., Lutz J.M., Usel M., Halter J., Stern M., Heim D., Rischewski J., Tichelli A., Gratwohl A. (Basel, Genf)

Introduction: Patients with a history of an allogeneic haematopoietic stem cell transplant (HSCT) have an increasing risk to develop a secondary cancer. The association of the HLA system to cancer is well known. Sibling donors share the same HLA alleles, and the question is, if they have an increased tumour incidence compared to the general population. This is of concern because the possibility of a tumour induction as a result of mobilisation with G-CSF has been discussed.
Methods: All HLA-identical sibling pairs with an HSCT from 1974 to 2001 for a malignant disease and living in Switzerland were evaluated. General data of the donors were taken from the patient's charts of the transplant unit. Donors were contacted per call or mail and asked about their current health status. In case of a malignant cancer, information on date of diagnosis,localisation,treatment was obtained. Data were compared with the age-,and sex adapted cancer incidence rate of the Swiss association of cancer registries (SACR). The same information was retrieved for the patients.
Results: 318 pairs were identified, in 291(92%) the donors (142 men (m), 149 women (w)) could be contacted. Median observation time was 13.8 years (y) (range 5–32 y). 146 donors were <50 y, 89 between 50–59 y, 29 between 60–64 y, 20 between 65–69 y and 7 >70 y old, hence 85% were <60 y old. Seventeen (6%) donors, 12 bone marrow and 5 peripheral blood donors, had developed a total of 18 cancer of 9 different localisations (mamma, prostate, skin, bone marrow, colon, bronchus, stomach, bladder, ORL). According to the incidence rate of the SACR, 3.3 tumours in m and 6.8 in w would have been expected, 3 (m) (RR 0.91) and 4 tumours (w) (RR 0.84) were found in donors between 0–49 y. In the age category 50–69 y, 4.5 tumours in m and 4.8 in w were expected and 5 (RR 1.11) respective 6 (RR 1.23) observed. In the subgroup of men between 60–64 y 1.07 tumour were expected and 4 observed ($p < 0.02$). No donor >70 y developed a tumour. 4 of the 291 donors had died, 3 from the tumour, 1 of cardiac disease. In 12 patients a secondary tumour was diagnosed post HSCT.

P140

Allogeneic hematopoietic stem cell transplantation (HSCT) in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

Studt J.-D., Buser A., Halter J., Heim D., Kappeler L., Lehmann T., Mattle H. P., Stern M., Tichelli A., Tiercy J.-M., Schüpbach M., Gratwohl A. (Basel, Bern, Geneva)

Background: MNGIE is an autosomal recessive disease characterized by ophthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral polyneuropathy, and leukencephalopathy, usually leading to death in early adulthood. It is caused by mutations of the ECGF1 gene encoding thymidine phosphorylase (TP) which result in virtual absence of TP activity, accumulation of thymidine and desoxyuridine, and subsequent instability of mitochondrial DNA. Reduction of thymidine and desoxyuridine levels is of therapeutic benefit, and was transiently achieved by transfusion of normal platelets. Experimental allogeneic HSCT has thus been reported since 2006 in two patients. Because of potential mitochondrial damage due to many drugs used during and after the transplantation procedure, allogeneic HSCT bears additional risks.
Patient and procedures: We report a 25 year old male patient suffering from MNGIE. His identical twin brother is also affected while a triplet sister is not. An older brother had already died from MNGIE. Allogeneic HSCT using bone marrow of an HLA 12 of 12 antigen matched unrelated donor was performed. Due to the metabolic alterations in MNGIE, increased drug toxicity was expected for substances with mitochondrial metabolization, e. g. nucleoside analogues, cyclophosphamide, paracetamole, certain antimetabolites, and azole antifungals. Reduced intensity conditioning as reported by Slavin et al. was therefore selected, consisting of fludarabine, intravenous busulfan, and anti thymocyte-globuline. Medication was adjusted and restricted carefully, and daily platelet transfusions were administered in order to provide TP substitution. To date, we did not observe relevant drug toxicity. Engraftment was at day 26. Apart from gastrointestinal bleeding occurring 6 weeks after HSCT, the subsequent course was uneventful without relevant infectious or immuno-

logical complications. No graft versus host disease was observed. Recovery of donor type hematopoiesis was normal 3 months after HSCT.
Conclusions: We report a patient with allogeneic HSCT for the treatment of MNGIE. The selected conditioning regimen did not result in an increased toxicity, and no relevant infectious or immunological complications were observed yet. This confirms allogeneic HSCT as a feasible therapeutic approach to MNGIE, provided a careful adjustment of conditioning and careful selection of medication. A longer follow up will be required to evaluate the impact on the disease course.

P141

Nephrotic syndrome after allogeneic hematopoietic stem cell transplantation: a rare renal manifestation of chronic graft-versus-host disease

Levrat E., Passweg J.R., Stucki A., Verholen F., Chalandon Y., Helg C. (Genève, Lausanne)

We report on two patients developing nephrotic syndrome (NS) after allogeneic hematopoietic stem cell transplantation (HSCT).
Patient 1: a 51-year old man underwent T-depleted HSCT after myeloablative conditioning from HLA-compatible unrelated donor for acute myelogenous leukemia M2.The immunosuppression was withdrawn on day 77, without sign of graft-versus-host-disease (GvHD). On day 188, the patient developed NS and kidney biopsy revelead a minimal change glomerulonephritis.The patient was treated with ciclosporine, prednisone, furosemide and lisinopril, with considerable improvement in proteinuria.
Patient 2: a 31-year old man underwent non T-depleted HSCT after nonmyeloablative conditioning from his HLA-identical brother for mediastinal large B cell lymphoma.His course was complicated 30 days later, during immunosuppression withdrawal, by development of cutaneous and digestive grade III acute GvHD and was treated with ciclosporine and prednisone, with response and progression in extensive muco-cutaneous chronic GvHD. Immunosuppression could be eventually withdrawn 6 years later. Seven months after withdrawal, the patient developed NS and muco-cutaneous GvHD exacerbation. The kidney biopsy revealed a membranous glomerulonephritis.The patient was treated with tacrolimus, mycophenolate mofetil, prednisone, and lisinopril, with complete remission of the NS at two years follow-up. Glomerular disease associated with NS is a rare complication of HSCT, most commonly in association with chronic GvHD.The glomerular histology most frequently reported is membranous glomerulonephritis, followed by minimal change glomerulonephritis. The temporal relationship between cessation or tapering of immunosuppressive medication and onset of NS, suggests that glomerular disease is a manifestation of the chronic GvHD and may, occasionally, be its only manifestation. Nonmyeloablative HSCT was identified as a risk factor for NS (especially membranous nephropathy, with basement membrane immune complex deposition) in one cohort study and it was then suggested that host B cells and plasma cells that survive reduced-intensity conditioning could play a role in the pathophysiology of this condition, who probably represents a humoral manifestation of chronic GvHD.The majority of reported cases in the literature have a relatively benign course with resolution or substantial improvement of NS following initiation of immunosuppressive therapy, as in our 2 case reports.

P142

Treatment of CLL with Alemtuzumab (MabCampath®) in a patient with dialysis dependent renal failure

Heizmann M., Bock A., Varga D., Bargetzi M.J. (Aarau)

Background: Alemtuzumab (A) is a human IgG1 molecule, which is not eliminated by dialysis (D). In this case report we describe for the first time the use of A in a patient undergoing D for chronic renal insufficiency.
Case report: A 67 y old female patient underwent therapy for CLL with 6 cycles of fludarabine and rituximab. In cycle 6 of this treatment, platelet count dropped to 9 G/l and a multithrombotic syndrome with acute renal failure and cerebral ischemic lesions developed. Renal biopsy revealed glomerular fibrin thrombi. There was no evidence for HIT, antiphospholipid syndrome or decreased levels of ADAMTS 13. Although hemolysis was not present, plasma exchanges resolved this situation and therefore the clinical picture was considered as secondary microangiopathic syndrome. A correlation to fludarabine was possible. The patient remained D dependent and was treated with hemodiafiltration (Fresenius FX 100 dialyzer, 3 x 4 hours per week, blood flow 400 ml/min). 26 months after the last cycle, relapse of CLL was observed in peripheral blood. Another 10 months later, therapy became necessary due to rapid doubling time of lymphocytes to 87 G/l in 2 months and generalized lymphadenopathy. Treatment with daily escalating doses of A (3, 10 and 30 mg) was begun and continued with 30 mg 3x/w. Each dose was given subcutaneously 60 minutes prior to D. Premedication consisted of clemastine 2 mg and paracetamol 1000 mg orally 60 minutes prior to A. During the first 3 weeks the patient received allopurinol 150 mg daily. Prophylaxis with Bactrim forte® 1 tablet 3x/w, valacyclovir 500 mg daily and fluconazol 200 mg 1x/w was given. Reactivation of CMV was monitored every two weeks by PCR, but remained undetectable. In the first weeks, treatment was well tolerated. Except for fatigue no additional symptoms occurred. Lymphocytes decreased rapidly to <0.1 G/l after only 5 days. Platelets fell transiently to 71 G/l and neutrophils to 1.1 G/l at nadir. Thrombocytopenia resolved after discontinuation of Bactrim. No fever or infection occurred. In week 8 of therapy the patient had repeated chills after injection and therefore refused further treatment. A total of 23 doses of A were administered. Results of remission status will be reported.
Conclusion: This case reports for the first time the safety and efficacy of treatment with alemtuzumab in a patient with D. The D procedure does not need to be modified in this setting.

P143

Regression of debilitating hypertrophic osteoarthropathy (HOA) by continuous nasal oxygen supplementation in a patient with severe, normoxaemic bronchiolitis obliterans (BO) after allogeneic hematopoietic stem cell transplantation

Halter J., Daikeler T., Cantoni N., Studt J.D., Stern M., Buser A., Häusermann P., Heim D., Tamm M., Gratwohl A., Brutsche M.H. (Hematology, Rheumatology, Dermatology, Pneumology Basel)

HOA is associated with periostitis, periarthritis, painful swelling and clubbing of affected limbs and evolve into a debilitating disease. It occurs as a paraneoplastic phenomenon, in the context of a chronic hypoxic heart or lung disease, or is associated with chronic liver disease and inflammatory bowel disease. Hypoxia is thought to mediate release of growth-inducing peptides. Treatment is mainly directed against the underlying disease. We report a 55 year old woman with BO who developed severe debilitating HOA. She had normal oxygen saturation as measured by repeated pulse oxymetry and arterial blood gas analyses. She was previously diagnosed with chronic myeloid leukemia blast crisis in 2004 and was treated with allogeneic hematopoietic stem cell transplantation from an HLA-matched unrelated donor after myeloablative conditioning with cyclophosphamid/busulfan. Acute cutaneous and intestinal graft versus host disease (GVHD) developed after transplantation and was treated with steroids. It evolved to chronic GVHD of the skin, oral and vaginal mucosa. In November 2006 severe BO developed after a respiratory viral infection still on low dose cyclosporine A. Despite intensified immunosuppression with tacrolimus, mycophenolic acid and steroids lung function remained severely impaired and deteriorated further after a pulmonary embolism four month later. She developed partial respiratory insufficiency with exercise-induced desaturation requiring intermittent nasal oxygen supplementation during physical efforts. Her oxygenation was normal at rest. After a stable disease course for further 6 months a painful swelling in several digits of both hands started to develop. Radiographically a periostal reaction and subcutaneous swelling was observed. Extramedullary leukemic relapse could be ruled out by biopsy. A bone scintigraphy revealed several sites of uptake. After exclusion of other possibilities, the diagnosis of HOA was made. Multiple attempts to control swelling and pain failed. Clinical signs and symptoms progressed. Despite documented normal oxygen saturation we postulated local tissue hypoxia and introduced a continuous oxygen supplementation (2 L/min via nasal cannula). About one week after initiation symptoms and swelling decreased with ongoing improvement since then.
Conclusion: Despite normal oxygen saturation local tissue hypoxia may have precipitated HOA in this patient with BO. Continuous application of oxygen proved to be a simple and in this patient very effective treatment. Pain, swelling and functional status of the digits improved and the patient is now able again to care for herself.

P144

Hematopoietic progenitor cell colony growth differentiates chronic myelomonocytic leukemia from reactive monocytosis

Stern M., Birrer A., Jusufi F., Meyer-Monard S., Bernimoulin M., Tichelli A., Gratwohl A., Nissen-Druey C. (Basel)

In the absence of a cytogenetic abnormality or overt dysplasia, chronic myelomonocytic leukemia (CMML) may be morphologically difficult to distinguish from reactive monocytosis. Definitive diagnosis of CMML is frequently based solely on the persistent presence of peripheral blood monocytosis without any underlying disease. We have previously described a typical growth pattern in CMML patients, i.e. “pseudonormal” colonies resembling granulocytic colonies but consisting entirely of monocytic cells when stained. To study the utility of the colony forming unit cell (CFU-C) assay as a diagnostic tool in patients with monocytosis, we analyzed a cohort of 48 consecutive patients referred to our institution between 1992 and 2005 with peripheral blood monocytosis. All patients had a complete haematological workup including bone marrow aspirate, histology and cytogenetics. Colony forming unit cells were analysed after two weeks culture in standard conditions using commercially available reagents. Median age at referral was 70 years; 17 patients were female, 31 male. Thirty-six patients fulfilled the WHO criteria for CMML; twelve patients were diagnosed with reactive monocytosis. Of the patients with CMML, twenty-eight showed pseudonormal growth with or without leukemic cluster growth, another four showed exclusively leukemic growth. None of the patients with reactive monocytosis showed either leukemic or pseudonormal growth. With a specificity of 100% and a sensitivity of 89%, the CFU-C assay had a unique potential to distinguish CMML from reactive monocytosis. The CFU-C assay using standard culture conditions is a highly sensitive and specific method to distinguish CMML from reactive monocytosis.

P145

ZAP-70 expression assessed by flow cytometry is a reliable, reproducible and predictive marker for IgVH mutation status in CLL patients if the ratio of B- to T-cell fluorescence intensity (“ratiometric method”) is taken into account

Solenthaler M., Schällibaum C., Horn M., Keller P., Oppliger Leibundgut E. (Bern)

ZAP-70 expression in B-CLL lymphocytes is a powerful prognostic marker and is strongly correlated to IgVH mutation status (IgVHms) as shown by gene expression profiling yielding concordance in 93%. However, methods assessing ZAP-70 expression by flow cytometry vary and results may differ considerably. Recently, a ratiometric analysis method based on comparison of ZAP-70 expression in B- and T-cells was described to circumvent intra-/interlaboratory variation, but cut-off values are not well established. On previously acquired data, we compared retrospectively our standard (healthy donor as an external control; cut-off >20% for positivity) with a ratiometric (mean fluorescence intensity of B-cells / T-cells x 100 [%]) analysis method (= “method”). If available, results were compared to IgVHms. ZAP-70 was measured in the peripheral blood of 104 pts. with SLL/CLL. The Mean + 3 SD of ZAP-70 expression of 84 normal controls was 21% (B-cells) and 19.9% (B-/T-cells) with the standard and ratiometric method, respectively. 37 pt. samples were ZAP-70 pos., 64 ZAP-70 neg. and 3 yielded borderline results. In 74 pts. IgVHms was available: 28 pts. had unmutated IgVH and 46 mutated IgVH. 80% of the ZAP-70 results were concordant to IgVHms (8 false pos., 8 false neg.) with the standard, and 76% (5 false pos., 14 false neg.) with the ratiometric method using the same cut-off (20%). However, ROC curve analysis was better for the ratiometric than for the standard method (AUC 0.84 with a cut-off of 13.2% and 0.77 with a cut-off of 22%, respectively). Combining both methods (cut-off >20% for ZAP-70 positivity using standard or ratiometric method, cut-off <= 20% or <=13.2% for ZAP-70 negativity using standard and ratiometric method, respectively, ratio = 1st priority) the concordance was 86% (5 false pos., 7 false neg.). 4 pts. had undergone ZAP-70 analysis at different time points with all results being concordant with the combined but not the standard method (2 pts. discordant). 11 samples were remeasured after a median of 161 (78-238) days and showed concordant results (Spearment’s coefficient with standard and ratiometric method 0.74 [p = 0.02] and 0.94 [p = 0.003], respectively). The performance of ZAP-70 expression analysis by flow cytometry in CLL patients can be improved by using the ratio of the B- and T-cell expression (“ratiometric method”). This may be due to methodology and/or by concomitant abnormal ZAP-70 expression in the T-cells of some CLL patients.

P146

Atypical presentation of acute myeloid leukemia: intracardiac AML

Rigamonti F., Beris P., Sanchez A., Passweg J., Chalandon Y. (Genève)

A 52 year-old man, presented with a 2 months history of dyspnea and was hospitalized with bilateral pleural effusion and cardiomegaly. An echocardiogram showed pericardial effusion with infiltration of infero-lateral cardiac wall, right auricle and aortic arch by a mass of unknown origin. Laboratory work up showed 1–2% blasts in the blood, but bone marrow aspiration was dry and 2 bone marrow biopsies did not show any leukemic infiltration. MRI of the heart showed infiltrative biventricular mass. Myeloid blasts that were MPO+ (21%) and had a 47 add(Y) (q12) 4 dim 9 caryotype were found in the pericardial and pleural effusion. A cardiac biopsy showed CD34+ cells in the myocardium. Flow cytometry analysis of the blood showed a blast population of CD34+, CD33+, CD13+ and HLA-DR+ cells which led to the diagnosis of extramedullary AML M1 or M2. Induction chemotherapy was with Cytarabine, Mitoxantrone and Etoposide. This was complicated by a cholecystitis, hemodynamic instability with arrhythmia (atrio-ventricular bloc type II), febrile neutropenia associated with mucositis grade 3. A control echocardiography 2 weeks after starting the treatment showed improvement with a decreased cardiac infiltration involving the left and right ventricles but associated with decreased ejection fraction to 40%. 4 weeks into induction chemotherapy, with persistent febrile neutropenia, the patient’s state deteriorated and he died of multiple parieto-occipital and thalamo-mesencephalic hypodensities associated with hemorrhage with breakthrough into the ventricular space and multiples spleens infarcts. Tumor embolism was suspected at this time as the patient had been treated with large spectrum antibiotics and antifungals and no culture had been positive. Autopsy revealed angioinvasive disseminated lesions involving the spleen, the brain and the heart caused by septic emboli, of probable fungal origin. There were no residual leukemic cells in the patient organs, with residual fibrotic scars in the myocardium. Extramedullary AML is a rare presentation also called granulocytic sarcoma or chloroma that may either precede or be concurrent with BM invasion. This may also be the first manifestation of relapse after chemotherapy or allogeneic HSCT. Cardiac infiltration is very rare, and in myeloid leukemia only a few cases of pericardial effusion, heart muscle infiltration or intracavitary masses have been described. The prognosis seems to be poorer than in de novo AML. The place of allogeneic HSCT as consolidation therapy is not well defined due to the paucity of data. Chemotherapy may be combined with local treatment such as radiotherapy or surgery. In a few reported cases, local therapy has been sufficient to control localized extramedullary AML mainly in extramedullary relapse AML without BM involvement. Extramedullary AML with cardiac involvement is a rare presentation of AML and rapid imaging associated with biopsy reveals the diagnosis.

P147

Hb H disease in combination with haemoglobin Pyrgos in a woman from Thailand

Rüfer A., Frischknecht H., Rovo A., Tichelli A., Wuillemin WA. (Luzern, Zürich, Basel)

We report a case of a 38-year old woman from Thailand who was referred for an evaluation of a microcytic, hypochromic anaemia with a haemoglobin of 98 g/l (normal range 115–148 g/l), MCV of 68fl (80–97 fl), MCH of 20 pg (27–34 pg) and MCHC of 298 g/l (330–364 g/l). Ferritin was normal (108 µg/l) and did exclude iron deficiency, and so were vitamin B12 and folic acid. The peripheral blood smear showed marked anisopoikilocytosis, microcytosis, hypochromasia, stomatocytes and a large number of target cells but no basophilic stippling. In the brilliant cresyl blue stain there were HbH inclusion bodies in 72% of the red blood cells. The high-performance liquid chromatography showed a reduced HbA and HbA2, an increased HbH of 6.1% and an abnormal haemoglobin of 56%. Using Gap-polymerase chain reaction the deletional mutations (—SEA) and (-[alpha]3.7) in the [alpha]-globin gene could be identified leading to the diagnosis of Hb H disease. In view of the abnormal haemoglobin the β-globin gene was sequenced and the β-globin variant haemoglobin Pyrgos (codon 83 GGC>GAC) was identified with no evidence of any other mutations in the sequenced area of the β-globin gene (–160 to +1620) excluding an additional β+-thalassaemia that could explain

the relatively high concentration of Hb Pyrgos. Hb Pyrgos was first described in a Greek boy but was later found in Thailand, too. All the carriers of Hb Pyrgos are clinically healthy. Coinheritance of Hb H disease and several other uncommon β-globin chains has been described. To our knowledge, this is the first description of a case of Hb H disease in combination with Hb Pyrgos without any other mutations in the β-globin gene. The clinical picture in this patient is determined by the presence of Hb H disease, which is in the deletional forms a mild disease although there is marked phenotypic variability. Iron overload, hepatosplenomegaly and cholelithiasis are common complications. The mild form of the thalassaemia in this case without iron overload could be explained by the presence of a β-globin gene defect decreasing the proportion of excessive β-globin chains. Folic acid supplementation is recommended in view of the usually mild haemolysis and increased erythropoiesis. In haemolytic crisis secondary to infection, aplastic crisis or during pregnancy transfusion of red blood cell concentrates may be required. Genetic testing of the partner and other family members for [alpha]- and β-thalassaemia carrier status is recommended.

P148

Hautveränderungen und Multiples Myelom

M. von Kietzell, M. Berger, S. Regenass, L. Weibel**, L. French**, U. Schanz, J. Fehr, J.S. Goede, G. Stüssi (Klinik für Hämatologie UniversitätsSpital Zürich, *Klinik für klinische Immunologie UniversitätsSpital Zürich, **Klinik für Dermatologie UniversitätsSpital Zürich)*

Wir präsentieren den Fall eines 41jährigen Patienten, der sich mit seit etwa einem Monat bekannter progredienter nekrotisierender Livedo racemosa und kutanen follikulären Spikulae auf der Dermatologie präsentierte. Zusätzlich bestanden Arthralgien, eine leichtgradige Anämie und B-Symptomatik. Der dermatologische Befund beschrieb multiple follikulär angeordnete harte weissliche filiforme Spiculae sowie eine Livedo reticularis an beiden Beinen mit multiplen, scharf abgegrenzten, dunkel-lividen Plaques mit Ulzeration und Blasen. Histologisch konnte an den Beinen eine leukozytoklastische Vaskulitis und am Rücken in den Follikelostien ortho- parakeratotische Hornpfropfen gezeigt werden. Aufgrund der typischen perifollikulären Spikulae wurde unverzüglich ein multiples Myelom gesucht: In der Knochenmarksuntersuchung konnte eine 75% Infiltration mit blastoiden Plasmazellen nachgewiesen werden, die Proteinelektrophorese und Immunfixation ergaben ein Paraprotein vom Typ IgG lambda von 42,7 g/l. Der konventionelle Röntgenstatus war unauffällig, die Nierenfunktion normal. Gleichzeitig konnte eine Kryoglobulinämie Typ I nachgewiesen werden. In der Aufarbeitung der biopsierten Spikulae konnten IgG-Ablagerungen nachgewiesen werden. Die ulcerativen Hautveränderungen wurden im Rahmen der Kryoglobulinämie interpretiert. Bei Diagnose des multiplen Myelomes (Stadium II nach Durie und Salmon) wurde mit Thalidomid/Dexamethason und begleitend Pamidronat begonnen. Hierunter konnte ein rasches Verschwinden der Spiculae und, unter ausschleichender Dauersteroidtherapie eine protrahierte Abheilung der ulcerativen Hautläsionen beobachtet werden. Trotz initial unauffälligem konventionellen Skelettröntgen kam es im Verlauf unter Therapie zu einer hyperkalzämischen Krise mit transientem Nierenversagen, worauf in einer CT-Untersuchung multiple Osteolysen nachgewiesen wurden. Bei progredientem Markbefall wurde auf Bortezomib, Adriamycin und Dexamethason umgestellt. Darunter konnte erstmalig eine Reduktion des Paraproteins nachgewiesen werden, das Restaging unter dieser Therapie ist noch ausstehend. Perifollikuläre Spikulae sind eine seltene kutane Manifestation des multiplen Myeloms. Das Phänomen wurde erstmals 1944 beschrieben, wobei bislang nur Myelome vom Typ IgG kappa oder lambda publiziert worden sind. Histologisch handelt es bei den Spikulae um verhornende Paraproteinablagerungen. In mehreren Fällen konnten gleichzeitig Kryoglobuline mit Livedo reticularis nachgewiesen werden.

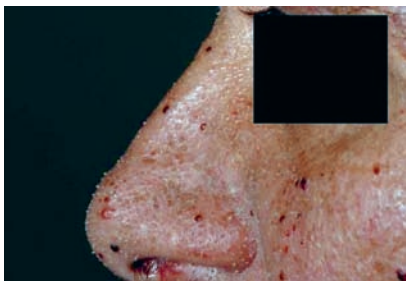


Abb. 1
Hautbefund

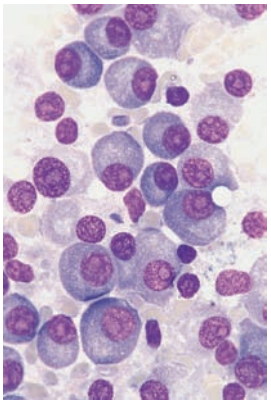


Abb. 2
Knochenmarksbefund

P149

Iron deficiency without anemia in young female blood donors: a reality that needs management

Waldvogel Abramowski S., Canellini G., Vedy D., Tissot J.D. (Lausanne)

Background: Blood donation leads to iron depletion. According to the recommendations in force, female donors safely could undergo 3 donations per year. Furthermore, iron storage, expressed by ferritin value, is significantly lower in pre-menopausal women than menopausal women. Menstruation is likely the main reason. In addition, iron supplementation, given to non-anemic women with low or borderline ferritin levels, has recently shown to decrease fatigue. This means, that subjective and negative symptoms can already be present before the onset of anemia. Here, we analyzed the impact of donations on ferritin level among women of reproductive age.
Patients, methods: During one month (October 2007), a pre-donation blood venous sample was collected in all female blood donors aged 18 to 50 years. Three groups were considered according to the frequency of blood donations in the last 12 months (group 1: 0 donation; group 2: 1 donation; group 3: 2 donations). Serum ferritin was measured by immuno-turbidimetry (Hitachi, Roche diagnostics, BSD Bern).
Results: 699 women were enrolled in the study and median age was 29 years. Three hundred and eight were included in group 1, 241 in group 2, and 150 in group 3. Mean ferritin level was 46 ng/ml, 33 ng/ml, and 24 ng/ml in group 1, 2 and 3, respectively. The difference was significant between each group (one way analysis of variance with Dunn's correction, $p<0.05$). The prevalence of iron deficiency without anemia (ferritin <16 ng/ml) was 9.4%, 19.1% and 35.3% in group 1, 2 and 3, respectively.
Conclusion: In pre-menopausal female volunteers, categorized according to the frequency of donations per year, the mean ferritin level significantly decreases. This result suggests that pre-menopausal women need more time than expected to compensate iron loss between two successive donations, and that a frequency of 3 donations per year might be too high. A new prospective study evaluating the individual negative effect of blood donation on iron store in this population is needed. A better understanding on how repeated donations affect female donor's health will allow to propose more appropriate recommendations (nutrition care and frequency of donations). Clinical and financial consequences of iron depletion for a donor are probably underestimated and should not be neglected.

P150

Severe pancytopenia in a 20 years old patient suffering from congenital apple-peel-syndrome

Redondo M., Spalinger J., Criblez D., Wuillemin W. A. (Luzern)

Background: Apple-peel-syndrome (APS) is a rare congenital disorder characterized by jejunal atresias, absence of a stomach membrane so that the small bowel twists around the left branch of the ileocolic artery.
Case report: We report a 20-years old male patient suffering from an APS. He developed a short bowel syndrome after abdominal surgeries necessitating parenteral nutrition for 16 years. On this regimen he developed severe liver fibrosis with portal hypertension and significant splenomegaly. Druing the following years the patient was weaned from TPN and enteral nutrition was successfully established. Stable pancytopenia (hemoglobin 133 g/l, leucocytes 1.4 G/l, neutrophiles 0.70 G/l, platelets 33 G/l) was observed for three years after starting enteral nutrition, most probably due to hyperplenisme. Within one year the patient then gradually developed severe megalobalstic anemia (hemoglobin 51 g/l, MCV 109 fl, MCH 37 pg, reticulocytes 49 G/l), agranulocytosis (leucocytes 0.5 G/l, neutrophiles 0.12 G/l), but still showed a stable platelet count (33 G/l). Vitamine B12- and folic acid-levels were normal, ferritin increased (1359 microg/l). Bone marrow showed increased cellularity with dysplastic changes of the myelo- and erythropoesis with sideroachrestic changes. The caryotype was normal. Furthermore, aceruloplasminemia and decreased copper plasma level of 0.5 micromol/l with normal urinary copper excretion (0.24 micromol/24 h) was found, consistent with copper-deficiency. After starting copper-substitution intravenously blood cell count returned to former values (hemoglobin 126 g/l, leucocytes 1.4 G/l, neutrophiles 0.82 G/l, platelets 48 G/l) within 16 days. MCV (95 fl) and MCH (34 pg) normalized within 2 months.
Discussion: Several mechanism may play a role in copper deficiency associated cytopenia. Downregulation of copper dependent enzymes lead to dysfunction of iron incorporation into the hem molecule (cytochrome C oxydase), downregulation of the superoxide dismutase causes increased damage of the red cell membrane by free radicals. The correction of MCV and MCH during copper-substitution suggests a copper-deficiency induced mechanism leading to a megaloblastic anemia.
Conclusions: Copper deficiency should be excluded in patients with cytopenia especially in patients with unaffected megakaryopoesis and normal cytogenetics, chronic gastrointestinal disorders or neurological signs of a copper deficiency.

P151

Not a simple hypermenorrhea

Colucci G., Alberio L., Keller P., Rüsges-Wolter I., Lämmle B. (Bern)

A 55-year-old woman was hospitalised in a peripheral hospital for hysterectomy because of uterus myomatosus and hypermenorrhea since one year. The bleeding history was otherwise negative. The recent medical history was characterized by cutaneous haematoma after mild trauma, depression, dyspnea during exercise, dysphagia and weight loss without a specific cause. A preoperative blood screening showed a normal platelet count (304G/l), a prolonged prothrombin time (Quick 30%) and a prolonged aPTT (158.1 s). The patient was transferred to our hospital. Coagulation analysis confirmed the results and showed additionally a prolonged thrombin time (33.2 s) and reptilase time (46.1 s), a low fibrinogen Clauss (0.42 g/l) and factor V:C (11%) and elevated factor II:C (138%), factor VII:C (173%), D-dimer (3472 'µ-g'/l) and thrombin-antithrombin-complex (47.0 'µ-g'/l). Factor X:C was normal (85%). A diagnosis of disseminated intravascular coagulation (DIC) was made. The patient received fresh frozen plasma and unfractionated heparin in a prophylactic dose. During hospitalisation coagulation parameters showed no significant changes and an extensive search of the cause of DIC was inconclusive. An extension of analysis showed a severely decreased '[alpha]-2-antiplasmin' (23%) and a therapy with tranexamic acid was started improving the fibrinogen and factor V:C levels. Hypothesizing that the cause of the DIC was a malignant tumor of the uterus, the patient was subjected to hysterectomy. Intra- and postoperatively no bleeding complication occurred. Postoperatively, coagulation markers still showed DIC. Because of dysphagia a gastroscopy with mucosal biopsy was performed. The Congo red staining showed multiple amyloid deposits and a diagnosis of primary AL-amyloidosis was made. The staging showed diffuse amyloid deposits within heart, marrow, colon, stomach and kidney. This case shows hypermenorrhea as first manifestation of DIC with pronounced fibrinolysis in the context of primary AL-amyloidosis with multiple organ involvement.

P152

Smouldering systemische Mastozytose als seltene Ursache einer rezidivierenden Flushsymptomatik

Dhayat N., Koltai E. (Solothurn, Laufenburg)

Hintergrund: Die systemische Mastozytose (SM) ist eine polymorphe Erkrankung mit Proliferation abnormer Mastzellen in diversen Geweben. Die Smouldering systemische Mastozytose (WHO-Klassifikation 2001) ist eine Unterform der indolenten systemischen Mastozytose.
Fallpräsentation: Der 50jährige Angestellte einer Tiefbaufirma beklagte seit drei Jahren eine chronische Diarrhoe sowie zunehmend häufiger auftretende Flushanfälle mit generalisierten Kribbelparästhesien, Hitzegefühl, Dyspnoe und unfreiwilligem Stuhlabgang.
Nach einem erneuten Flushanfall mit Präkollaps, Schwindel und Kopfschmerzen blieb die Symptomatik trotz einer stationär durchgeführten Diagnostik mit Ausschluss gängiger Flush-Ursachen wie Karzinoid und Phäochromozytom bei klinisch lediglich feststellbarer passagerer Hautrötung weiterhin unklar.
Diagnostik: Erst eine ambulante systematische Diagnostik mit der Suche nach seltenen Flush-Ursachen erlaubte die Diagnosestellung einer Smouldering systemischen Mastozytose durch folgende Befunde: kleinknotige Infiltration des Knochenmarks mit atypischen, CD2/CD25 positiven Mastzellen, Nachweis der c-Kit-D816V-Punktmutation, Erhöhung der Serumtryptase, Osteoporose der LWS Knochendensitometrie) und Splenomegalie (Abdomencomputertomographie). Als wahrscheinliche Triggerfaktoren wurden körperliche Anstrengung sowie ein exzessiver Bierkonsum identifiziert.
Therapie und Verlauf: Unter der Therapie mit einem H1- und H2-Rezeptor-Blocker sowie Alkoholrestriktion sistierten sowohl die Diarrhoe als auch die Flushanfälle inklusive Begleitsymptomatik. Die Osteoporose wird mit Calcium, Vitamin D und einem Bisphosphonat behandelt. Wegen der Gefahr von anaphylaktischen Reaktionen wurde ein Adrenalin-Auto-Injektor abgegeben. Regelmässige Kontrollen sind indiziert, da eine Krankheitsprogredienz mit Übergang in eine aggressive SM möglich ist.
Schlussfolgerung: Die Differentialdiagnose von Flush-Reaktionen ist sehr umfangreich und es bedarf häufig einer systematischen Diagnostik. Aufgrund der vielfältigen klinischen Präsentation wird die Diagnose einer SM oft nicht gestellt. Das Fehlen einer Urticaria pigmentosa, die bei der indolenten SM in über 90% der Fälle vorkommt, verzögerte hier die Diagnosestellung erheblich. Die Therapie mit einem H1- und H2-Blocker führte im vorliegenden Fall zu einer Symptomkontrolle.

P153

Inhibition of the myeloid tumor suppressor p15INK4b by the centrosomal protein CEP70

Tschan M.P., Shan D., Arvidsson G., Tobler A., Fey M.F. (Bern)

A role for $p15^{INK4b}$ (hereafter p15) in myelopoiesis is suggested by the frequent loss of its expression in myeloid malignancies. A common p15 silencing mechanism in acute myeloid leukemias (AML) and in myelodysplastic syndromes is promoter hypermethylation. Further, the INK4b locus is directly silenced by the fusion gene product CBFβ-SMMHC in inv(16)$^+$ AML samples. Interestingly, the INK4b locus encodes two transcript variants, p10 and p15, both showing similar inhibitory effects on cell growth. In an attempt to find direct regulators of p10 and p15, we performed a yeast two-hybrid screen. We identified the centrosomal protein CEP70 as new binding partner of p10. Preliminary gene expression studies using RT-PCR revealed that CEP70 is frequently expressed in myeloid leukemic cells and healthy CD34$^+$ progenitor cells but not in normal granulocytes or macrophages. In line, PMA- and ATRA-induced differentiation of U937 myeloid leukemic cells towards macrophage- or neutrophil-like cells resulted in downregulation of CEP70 mRNA paralleled by an increase of p10 and p15 mRNA as measured by real-time RT-PCR. To further investigate a role for CEP70 in myeloid differentiation, we generated U937 CEP70 knockdown cells using lentivirus delivered shRNA. Upon PMA treatment these cells showed markedly enhanced macrophage development compared to control shRNA expressing cells as assessed by morphology. Moreover, p10 and p15 protein levels were significantly higher induced in PMA-treated CEP70 knockdown as compared to control cells. In addition, U937 CEP70 knockdown cells displayed significantly less cell death during PMA treatment than control cells as shown by XTT assays.
In summary, we identified CEP70 as a new binding partner of p10/p15 and demonstrate that downregulation of CEP70 is needed for macrophage differentiation to occur in leukemic cells. We propose a model where high CEP70 expression contributes to a leukemic phenotype by inhibiting p10 and p15. Current experiments aim at deciphering how the inverse regulation of these genes during myeloid development affects centrosome function.

P154

Crosstalk between human mesenchymal stromal cells and allogenic natural killer cells

Pradier A., Villard J., Passweg J., Kindler V. (Geneva)

Background: Mesenchymal multipotent stromal cells (MSC) are postnatal stem cells that can inhibit steroid-resistant graft-versus-host-disease (GVHD) occurring after allogenic hematopoietic stem cells transplant. Natural killer cells (NK), infused once GVHD has subsided, can eradicate the eventual leukemia relapse provoked by immune suppression. So far the interplay between MSC and NK is not fully understood. For this reason, we investigated the interactions between MSC and NK in vitro.
Methods: NK were purified from buffy coat by Ficoll-Hypaque gradient centrifugation and negative selection using immuno-labeled magnetic beads. MSC were isolated from femur heads of patients who underwent hip replacement surgery. CFSE-labeled NK were cultured in a medium supplemented with 5% platelet lysate with IL-15 (0–25 ng/ml) in absence or presence of MSC. After 6 days NK proliferation was assessed by CFSE dilution. NK cytotoxicity was tested using a flow cytometry based assay.
Results: Optimal proliferation of NK was achieved using 25 ng/ml of IL-15 (87% CFSE low cells). This value was reduced to 40% in presence of MSC (n = 5, p = 0.008, Mann-Whitney). However in these conditions, NK were cytotoxic towards the MSC stroma. By contrast, preliminary experiments (n = 2) performed under conditions that sustained NK survival but not proliferation in absence of MSC, showed that NK proliferation could be triggered by MSC. This suggested that MSC could also have a proliferative effect on NK.
Conclusion: These in vitro data indicate that the effect of MSC on NK correlates with the activation status of the later, a fact that is consistent with in vivo observations on leukemic patients. Infused MSC inhibit acute GVHD but are rarely detected in vivo, suggesting that NK initially co-injected with the hematopoietic stem cells, optimally activated by the GVHD possibly kill them. By contrast delayed allogenic NK infusion performed after GVHD has settled down, efficiently eradicates relapsing leukemia without inducing generalized inflammation or impairing hematopoiesis. As hematopoiesis depends on functional host MSC, this suggests that when inflammation is low, NK do not kill host MSC. Moreover NK are not inhibited by MSC as they can effectively eradicate the residual leukemic cells. Further understanding the crosstalk between MSC and NK has to be achieved before cell therapies involving both cell types can be envisaged.

P155

Cryohydrocytosis: Increased activity of cation carriers in red cells from a patient with a band 3 mutation

Goede J.S., Bogdanova A., Weiss E., Bernhardt I., Lutz H.U. (Zurich, Saarbrücken)

Cryohydrocytosis is a dominantly inherited hemolytic anemia with a phenotype easily leading to the misdiagnosis of spherocytosis. The red blood cell (RBC) membranes from most cryohydrocytosis patients contain normal stomatin levels, but mutations in a transmembrane segment of the band 3 protein, the anion-transport protein (Bruce et al. 2005. Nat Genet 37:1258–1263). Transfection experiments suggested that the mutation in the anion exchanger may convert the anion exchanger into a non-selective cation channel. Unexpectedly, RBCs from one of these patients with the mutation H734R in band 3 showed instead a rather controlled permeability increase. Outside sodium ions prevented, while outside potassium ion enabled the cold-induced swelling as studied by density gradients and ektacytometry. The swelling was not inhibited by the anion-transport inhibitor DIDS. Measurements of the changes in cellular ion and water content revealed that in NaCl-containing medium Na+/K+ exchange prevailed whereas in potassium-containing medium swelling was mediated by chloride-dependent potassium uptake. Unidirectional potassium influx measurements showed that the cells have abnormally high activities of the K+(Na+)/H+ exchanger and K+,Cl-cotransporter that could account for the net movements of cations in NaCl and KCl-containing media. These results suggest that a mutation-mediated cross-talk between band 3 and other transporters might increase cation permeability in cryohydrocytyosis.

P156

Ultrafine diesel exhaust particles affect collagen-induced platelet aggregation in a bimodal way

Forestier M., Sauvain J.J., Büchi L., Beer J.H. (Baden, Lausanne)

Background: There is robust evidence that air pollution with fine (<2.5 μm; PM2.5) and ultrafine (<0.1 μm; UFP) particles are dose-dependently associated with an increased incidence of cardiovascular events and a progressively reduced pulmonary function. Mechanisms include an inflammatory cytokine response and an elevated procoagulant activity by alveolar macrophages and endothelial cells.
Hypothesis: We hypothesized that a direct platelet activating effect by Diesel exhaust particles (DEP) could be operative since they easily pass epi- and endothelial barriers. They may cause platelet activation and may also contain divalent heavy metal ions, some of which are known to activate GPIIb/IIIa (Zn^{++}, Ca^{++}, Mn^{++} etc.).
Methods: DEP was provided as standard SRM 1650 from the National Institute of Standards and Technologies and was reconstituted in saline/0.1% Tween 20. Incubation of citrated normal whole blood from healthy donors was performed for 60 min at room temperature in the presence of 0.1 μg/ml DEP or vehicle, which corresponds to a daily absorbable respiratory dose of DEP. The DEP concentrations were increased stepwise 25–50 fold and platelet aggregation in platelet rich plasma (PRP^{250}) was analyzed vs. control samples in a PACKS-aggregometer (Helena) with collagen, convulxin, ADP, ristocetin and arachidonic acid at typical standard concentrations. A collagen concentration was chosen which induced a 70% aggregation (2.5–5 μg/ml).
Results: At daily respirable concentrations of DEP (0.1 μg/ml), collagen-induced aggregation was enhanced by 52 ± 9% (± S.E.M., p <0.01, n = 5), while higher DEP concentrations of 2.5–5 μg/ml led to an inhibition of collagen induced aggregation by ~40 ± 10% (p <0.05, n = 8). The ADP-, arachidonic acid- and ristocetin-stimulated aggre-

gation remained unaffected. Similarly as with collagen, the convulxin-induced platelet aggregation was reduced by ~30% with the higher DEP-concentrations.
Conclusion: DEP appears to influence collagen-induced platelet aggregation. The stimulatory low dose effect is compatible with the hypothesis and the clinical literature. The inhibitory effect at high doses may be due to an interference with platelet GPVI, since convulxin-induced aggregation is selectively affected as well. Mechanisms are under investigation.

P157

Thalidomide increases tissue factor activity on human umbilical vein endothelial cells in vitro

Valsami S., Leikauf M.S., Madon J., Fehr J., Asmis L.M. (Zürich)

Background: Current treatment protocols for multiple myeloma include thalidomide. In the presence of varying thromboprophylactic regimens, thalidomide treatment of myeloma patients is associated with a high rate of venous thromboembolic events. The reported event rate varies with co-medication including dexamethasone and chemotherapy and ranges from 3 to 28%. Tissue factor (TF) is the cellular receptor for clotting factor VII/VIIa and plays a central role in the initiation of coagulation in vivo. Presently there is no consensus regarding the optimal thromboprophylaxis strategy.
Study Hypothesis: Thalidomide alters endothelial thromboresistance by increasing TF expression and function. Co-medication modifies the thalidomide-induced effect.
Materials and Methods: We examined functional TF expression, induced by thalidomide (Lipomed, Sigma) alone or in combination with dexamethasone (Sigma), in human umbilical endothelial cells (HUVEC, Lonza), under inflammatory conditions (in the presence of TNFα), using functional coagulation assay (Actichrome TF, American Diagnostica). HUVEC were of passage 5–8, cultured for 3 days, incubated for 24 hours and examined under sub-confluent conditions. Thalidomide and dexamethasone concentrations used were similar to therapeutic human plasma levels. Each experiment was repeated at least 3 times.
Results: Constitutive TF activity in HUVEC is at the limit of detection. TNFα induced an approximately 10-fold increase in functional TF expression. In our study thalidomide, tested in three different concentrations, up-regulated TF coagulant activity under TNFα-induced inflammatory conditions. Thalidomide at a concentration of 0.5 μM induced a 25% mean increase of TF expression in each of 7 experiments. Higher concentrations of thalidomide (5 and 50 μM) also increased TF expression compared to control but less than 0.5 μM. The addition of dexamethasone modulated TF expression in a non-synergistic way.
Conclusions: According to our data thalidomide increases TF procoagulant activity in endothelial cells in vitro. This TF up-regulation by thalidomide may also occur on endothelial cells in vivo and could thus be one of the underlying mechanisms of hypercoagulability in patients with multiple myeloma receiving thalidomide containing regimens.

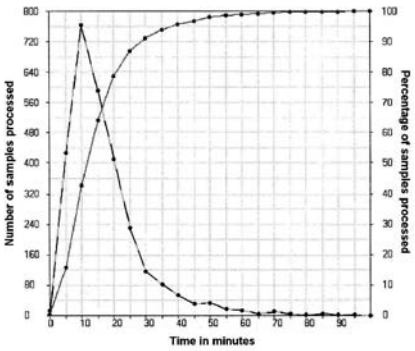
P158

Total automation of peripheral blood cell analysis in a University Hospital can provide rapid and high quality results to specialized departments and avoid the need of satellite point-of-care laboratories

Tichelli A., Rovó A., Schellhorn R., Marbet G., Meyer-Monard S., Arber C., Medinger M., Tsakiris D., Freidank H., Gratwohl A. (Basel)

A hematology laboratory of a University Hospital with diverse high performance specialties requires an efficient, rapid and high quality system for the routine analysis of peripheral blood counts. However, speed and high quality results often seem incompatible. Implementation of point-of-care satellite laboratories in emergency departments and hematology-oncology units appears attractive but is split from integrative quality mechanisms. Hence, point-of-care testing provides only simple results frequently with lower quality. In contrast, centralized specialized hematology core labs need more time to bring out results but supply very reliable and specialized results. We intended to combine both advantages, speed and high quality by introducing a fully automated hematology system, with 2 analyzers, performing complete blood counts, 5-part differential, reticulocytes, and scattergrams (Advia 2120®). Each analyzer was linked to an automated slide maker and strainer (Autoslide®) and connected to a robotic street system offering a continuous flow processing, specimen distribution to the instruments, and tube collection at the end of the testing.
A user-defined reflexive system initiated reticulocytes or slide making in case of abnormal values. An electronic workstation (CentraLink®) collected data from all instruments for validation and release. In order to optimize turnaround time, automated validation and release was organized for technically unproblematic results. The automation was initiated in Sept. 2007 achieving full work capacity in <2 months. The system works now in routine, 7 days a week, 24 hours a day. Within a standard 7-day week, the performance of the system was 2950 complete blood counts, 305 reticulocytes, and 337 slides. Ninety-nine (32%) of the reticulocytes and 175 (52%) of the slides were initiated by the reflexive system. From all blood counts, 2310 (78%) were validated and released automatically, 640 (22%) were withhold to be validated manually. The time taken for the laboratory to process a sample from admission to release on the central lab computer system is illustrated in the figure. Ninety-one percent of the samples were released within 30 minutes. These data prove that high technology equipment with appropriate management can fulfill the requirements for speed and high standards of an integrated quality system in a University Hospital with high complexity. In near future routine coagulation tests will be integrated on the system.

Figure 1
Turnaround time of a sample from admission in the lab to release on the lab computer. The continuous line represents the cumulative percentage of the samples processed by time and the dotted line the number of samples processed by time.



P159

A hook in the ferritin measurement in patients with hemophagocytic syndromes

Keller P., Aregger F., Wermuth B., Lämmle B. (Bern)

Extensively increased serum ferritin levels are a hallmark of hemophagocytic syndromes. However, most commercially available ferritin assays are optimized to rapidly detect low ferritin levels in the setting of iron deficiency. We report on two patients with highly active hemophagocytic syndrome and erroneously normal ferritin levels. Patient A was initially diagnosed with hemophagocytosis because of greatly increased ferritin levels. When a high grade non-Hodgkin lymphoma was found and successfully treated, symptoms resolved and ferritin normalized. Four month later, the patient presented with symptoms similar to the initial presentation. However, ferritin was only 270 [mikro]g/l. After talking to the laboratory, the serum was diluted, remeasured and the result corrected to 598'000 [mikro]g/l. In patient B, the treating physician suspected a hemophagocytic syndrome, but serum ferritin was only 146 [mikro]g/l. We again informed the laboratory. After remeasuring ferritin using serum dilutions, the ferritin value was corrected to 4225 [mikro]g/l. Many automated ferritin assays are variants of the classical sandwich-ELISA. A solid phase-immobilized anti-ferritin antibody captures the antigen from the test serum. Simul-

taneously or timely delayed, but without prior washing, a second, labeled anti-ferritin antibody is added. In a washing step, all labeled antibody which is not bound to the solid phase through the first antibody and the antigen, is washed away. Finally, chemiluminescence or an enzyme reaction on the detecting antibody reflects the amount of bound antigen. Automated immunoassay systems are often not designed to include a washing step before adding the second antibody. With very high excess of antigen, the capturing antibody is saturated and most labeled detecting antibody is bound to free ferritin in the serum and will be lost with the final washing step, leading to erroneously low or even normal ferritin values. This phenomenon was first described by Miles et al. in 1974 with an immunoradiometric assay. Today known as "Hook-effect", it imposes a potentially dangerous problem in many immunoassays in the clinical laboratory. Clinicians have to be aware of the possibility of erroneously low ferritin results in the diagnostic work-up of hemophagocytic syndromes. If hemophagocytic syndrome is suspected, the laboratory has to be informed and the measurement must be repeated with appropriately diluted sera.

P160

Citrate toxicity in healthy donors for allogeneic peripheral blood stem cell (PBSC) donation

Sigle J., Stern M., Infanti L., Halter J., Gähler A., Buser A., Gratwohl A. (Basel)

Objective: Citrate toxicity is the most common adverse event of apheresis. Intravenous (iv) Ca-supplementation significantly reduces its incidence. A Ca supplementation rate >0.5 mg Ca/ml ACD has been proposed. We evaluated incidence and severity of citrate related side effects and analysed contributing factors in donors undergoing PBSC apheresis for allogeneic HSCT at our institution.
Methods: We analysed 68 collection procedures between October 2003 and October 2007 involving 53 donors (24 male, 29 female; median age 49 years). All donors received iv Ca-supplementation. Side effects were graded as mild (paraesthesia/flushing), moderate (nausea/vomiting) or severe (tetany/seizure).
Results: Citrate toxicity occurred in 40/68 procedures (59%), 37 mild, 3 moderate. In univariate analysis, side effects were more frequent in females (76% vs 37% in males, p = 0.001). Patients suffering from side effects had a smaller body surface area (BSA, median 1.69 vs 1.94 m^2, p <0.001) and smaller apheresis flow volume per minute (53.2 vs 61.4 ml/min, p = 0.001). After normalization to BSA, quantity of citrate infused (55 vs 54 mg/min/m^2, p = 0.89) and initial calcium infusion rate (1.21 vs 1.12 mg/min/m^2, p = 0.26) were not associated with side effects. Baseline albumin-adjusted serum calcium and donor age were not associated with side effects. Patients receiving calcium substitution at an initial rate of 0.5 mg Ca/ml ACD or higher showed side effects at a comparable frequency to those receiving lower dose Ca supplementation (57% vs 62%, respectively, p = 0.87). In multivariate analysis, only female sex remained associated with occurrence of side effects (OR vs males 4.67, 95% CI 1.47–14.9, p = 0.009). Within the groups of female and male donors, those with small BSA (below median) showed comparable rates of side effects to those with large BSA, confirming the results of multivariate analysis and suggesting that the increase in side effects in small BSA donors was mainly due to a high frequency of females.
Conclusion: Despite routine intravenous Ca-supplementation, citrate-related side effects were frequent in donors undergoing apheresis for allogeneic HSC collection. Neither calcium supplementation rate, citrate infusion rate, nor their ratio predicted side effects. Female gender emerged as main risk factor for citrate mediated side effects. The pathophysiological mechanism for this observation remains unclear.

P161

Febrile neutropenia and unexpected pathogens in bone marrow smear... so what?

Schmidtko J., Solenthaler M., Garzoni C., Hahr M., Demarmels Biasiutti F., Keller P., Alberio L., Lämmle B., Colucci G. (Bern)

A 24-year-old, one year ago kidney transplanted patient was hospitalized because of febrile neutropenia without focus. His recent medical history was characterized by an aphthous ulcer in his mouth and a progressive hyporegenerative anemia. The immunosuppressive therapy consisted of cyclosporine, mycophenolate mofetil and steroids. History and clinical examination were unremarkable, in particular no signs of sepsis were present. C-reactive-protein was 36 mg/l. Repetitive blood cultures and serologic testing for CMV, EBV, Parvovirus B19 and HIV were negative. Urine culture remained sterile. A bone marrow aspiration was performed and showed only in one out of 4 smears a region with dense accumulation of bacteria, microscopically with different morphology (coccoid- and rod-like), plus monomorphic unidentifiable cells that were possibly not bone marrow derived. An empirical antibiotic therapy with cefepime and metronidazole was started. The clinical situation remained stable. The finding of massive bacterial invasion of the bone marrow was in contrast to the stable clinical condition of the patient and a repeated bone marrow aspiration did not show any bacteria. Bone marrow cultures as well as an eubacterial PCR using 16S rRNA amplification performed on bone marrow material were negative. The bacterial distribution on the smear was drop-like and the unidentifiable cells described were compatible with enzymatic damaged bone-marrow cells. This finding was interpreted as an external contamination during bone marrow smear processing. Confronted with unexpected laboratory results, a critical and comprehensive interpretation is needed. Pathologic results have to be correlated with the clinical conditions. Contamination of diagnostic material should always be considered because of its possible consequence related to unnecessary diagnostic procedures and therapy, as well as an increase in costs.

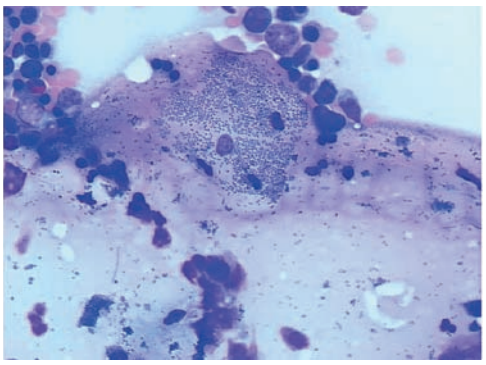


Figure 1
Dense accumulation of bacteria

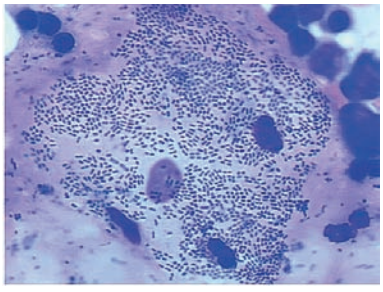


Figure 2
Enlarged

P162

Pharmacokinetics of dalteparin in prophylactic dosage in patients with impaired renal function

Schmid P., Brodmann D., Fischer A.G., Wuillemin W.A. (Luzern)

Background: Low molecular weight heparins (LMWH) are safely used for prophylaxis of venous thromboembolic disease. Impaired renal function limits their use due to accumulation. The aim of this study was to clarify the pharmacokinetics of dalteparin in patients with renal insufficiency (RI).
Methods: Inpatients of a medical and surgical department with all stages of RI (including peritoneal dialysis patients) were included into a prospective observational cohort study. Glomerular filtration rate (GFR) was estimated using plasma creatinine. Peak plasma anti-Xa activity (AXa) was measured every 3 days and adjusted to applied dalteparin dose and body weight. Data are shown as median (interquartile range).
Results: Data of 42 patients (26 men) with all stages of RI could be analyzed. Since there were only few peritoneal dialysis patients and long term use of dalteparin, data of dialysis patients are shown separately. Median follow up of non dialysis patients (36 patients, 21 men) was 10 days (range 4–20). Three groups were defined according to renal function (A to C, see table 1 for definitions). The median daily dalteparin dose was 74 (62–85) units / kg body weight without difference between the groups (p = 0.33). Adjusted anti-Xa values are shown in table 1 and figure 1 for days 1 and/to 10. Relative increase (i.e. accumulation) of adjusted anti-Xa from day 1 to 10 was not different between the groups (table 1). Median follow up of peritoneal dialysis patients (CAPD, 6 patients, 5 men) was 5.5 days (range 4–19). Median daily dalteparin dose was 58 (44–69) units / kg body weight. Adjusted anti-Xa values are shown in figure 1. They were at day 4 for patients with CAPD 5.9 $x10^{-3}$ (4.8–6.4) compared with patients without RI 3.9 $x10^{-3}$ (2.9–4.6; n = 0.008). Relative increase from day 1 to 4 was 17.5% (4 to 45) for CAPD, and 3.5% (–19 to 27; p = 0.48) for patients without RI, respectively. However, there were 2 patients up to 10 days and one patient up to 19 days with CAPD without signs of clinically significant accumulation.
Conclusion: The use of dalteparin in prophylactic dosage showed no clinically significant accumulation even in patients with severely impaired renal function during median follow up of 10 days (range 4–20). Data showed that dalteparin may be suitable even in peritoneal dialysis patients, although further studies of long term application are needed in this population.

Table 1: Adjusted AXa (expressed in values $x10^{-3}$) for days 1 and 10, and relative increase, i.e. accumulation (median, interquartile range)

GFR in mL/min/1.73 m²	Day 1	Day 10	Relative Increase (= Accumulation)
A (GFR ≥ 60), n=15	3.8 (3.2 – 4.6)	3.9 (3.4 – 4.6)	14% (7 to 35)
B (GFR 30-59), n=14	4.1 (3.7 – 5.5)	6.1 (5.3 – 7.6)	11% (-3 to 55)
C (GFR <30), n=7	3.9 (3.1 – 4.6)	4.9 (4.2 – 5.6)	23% (0.5 to 31.5)
	A vs B: p=0.35 A vs C: p=0.91	A vs B: p=0.007 A vs C: p=0.17	A vs B: p=0.95 A vs C: p=0.91

Table 1

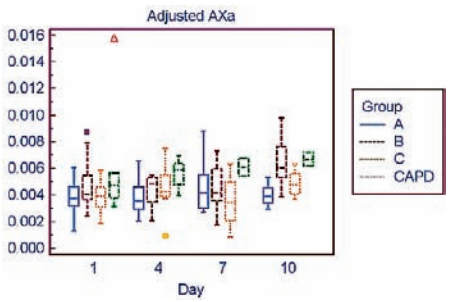


Figure 1
Adjusted peak anti-Xa activity (AXa) for days 1 to 10

P163

Monitoring thrombin generation by a newly developed electrochemical method identifies patients at high risk for recurrent venous thromboembolism

Thürlemann C., Demarmels Biasiutti F., Lämmle B., Alberio L. (Bern)

Background: Screening patients after a first VTE for thrombophilia is common clinical practice in order to optimize the long-term treatment. Recently, G. Hron et al. (JAMA 2006;296:397) demonstrated that measurement of thrombin generation (TG) identifies patients at low risk for recurrent VTE. We have developed a Biosensor-System determining TG by electrochemistry. With this system coagulation can be activated either extrinsicly (test strips A) or intrinsicly (test strips B). We aimed to investigate the relationship between our new procedure and VTE recurrences.
Method: In a retrospective cohort study we recorded TG in plasma samples of 75 patients who had suffered a first idiopathic VTE. Oral anticoagulant therapy (OAT) was discontinued at least one month (median 2 months, inter-quartile range 1.3–3.6 months) before thrombophilia screening. Median follow-up was 9.0 years (iqr 7.4–11.5 years). During this period 16 patients (21%) suffered recurrent VTE at a median of 5.7 years (iqr 4.2–8.4 years) after cessation of OAT. We investigated the following TG parameters with our electrochemical Biosensor-System: lag-time (t-lag), time to maximum slope (tS-max), value of maximum slope (S-max), time to peak (t-max), maximum electric current, i.e. peak height (I-max), and ratio I-max / t-max (TG-rate).
Results: A combination of two TG parameters, 'TG-rate' (test strips A) and 't-max' (test strips B), allows to identify patients with high risk for recurrent VTE. Among 7 patients whose plasma samples showed a 'TG-rate' greater than 0.14 and a 't-max' shorter than 515 seconds, 6 (86%) suffered recurrent VTE versus 10 (15%) out of the remaining 68 patients (P <0.001).
Conclusions: Our Biosensor-System recording thrombin generation by electrochemistry allows to identify patients at high risk for recurrent VTE.

P164

Stored erythrocytes have less capacity than normal erythrocytes to support primary hemostasis

Zehnder L., Schulzki Th., Hayes J., Reinhart W.H. (Chur, Davos)

Background: Primary hemostasis after vessel injury is mediated by platelet aggregation. Red blood cells (RBCs) are involved in this process by pushing platelets towards the vessel wall during flow and allow platelet adhesion. We hypothesized that stored RBCs could have less capacity to support primary hemostasis by this way.
Methods: RBC units from 17 healthy volunteers were used. After 45 days of storage at 4°C, fresh citrated blood was taken again from the same donors. Platelet-rich plasma (Platelet count 178 ± $40x10^3$/µ-l) was prepared, in which RBCs were resuspended with a constant hematocrit (40%), but changing fractions of stored versus fresh autologous RBCs (0, 25, 50, 75, and 100%, respectively). A platelet function analyser PFA-100® was used to measure primary hemostasis. This instrument closely simulates in vivo conditions with blood flowing at high shear rates through a membrane pore, which is coated with collagen and either epinephrine (EPI) or ADP. Platelets, which are pushed towards the wall by RBCs, adhere, aggregate, and form an occluding plug, which stops blood flow and is measured as closure time (CT).
Results: With increasing fractions of stored blood, the CT increased. CT-EPI was 121 ± 17s for 100% fresh and 0% stored RBCs, 129 ± 32s for 25% stored RBCs, 164 ± 45s for 50%, (p <0.0001 compared with 0% stored RBCs; ANOVA), 214 ± 54s for 75% (p <0.0001), and 273 ± 36s for 100% stored RBCs (p <0.0001). For CT-ADP the values were 91 ± 22s, 95 ± 12s, 101 ± 13s, 124 ± 44s (p = 0.004), and 191 ± 72 s (p <0.0001) for 0. 25, 50, 75, and 100% stored RBCs, respectively.
Conclusions: Stored RBCs have less capacity than normal RBCs to support primary hemostasis by platelet aggregation, suggesting a decreased capacity of stored RBCs to bring platelets into close contact with the wall to which they adhere. This mechanism may contribute to sustained bleeding seen after mass transfusion.

P165

Efficacy of lower dose recombinant factor VIIa for massive bleeding in off-label use

Schmid P., Lämmle B., Alberio L. (Bern)

Background: Recombinant factor VIIa is increasingly used for uncontrolled bleeding in patients without a pre-existing haemostatic disorder (off-label use). There is no clear evidence of the benefits of this practice. Furthermore, the minimal effective dosage is not clear yet. In order to optimize the use of rFVIIa at our institution we suggest to administer 60 mcg/kg body weight for controlling massive bleeding in off-label use.
Methods: Prospective cohort study collecting data of all patients treated with rFVIIa in 2005 and 2006. Statistical analysis was done with MedCalc. Values are given as median (interquartile range).
Results: Fifty-seven patients received rFVIIa off-label (total dose 286.6 mg). Clinical categories were: surgery 35%, obstetrics 23%, trauma 21%, medicine 9% (unknown 12%). The administered single dose was 64 (56–74) mcg/kg. The majority of the patients (82%) received rFVIIa once, 18% twice. Severe haemorrhage was documented before rVIIa administration: estimated bleeding rate 850 (308–2500) mL/h, volume replacement with 4.0 (3.0–5.5) L crystalloids and/or colloids, 10.5 (6–16.5) units packed red blood cells (RBC) and 8 (4–14) units fresh frozen plasma. According to the treating physicians a bleeding rate reduction was observed in 86% of the patients and a quantitative estimate of the bleeding rate showed a significant reduction ($p = 0.002$; figure 1). Transfused packed RBC significantly decreased, as well ($p < 0.001$; figure 2). Median fibrinogen at time of rFVIIa administration was 1.30 (0.75–1.85) g/L; response to treatment was similar in both patient groups with fibrinogen lower or higher than 1 g/L. Interestingly, there was a clear trend for better treatment response if tranexamic acid was given in addition to rFVIIa. There was only one venous thrombo-embolic complication reported (patient without tranexamic acid). Eight patients (14%) died during the first 24 h: 40% among medical, 25% among trauma, none among surgical and obstetrical patients.
Conclusion: A single injection of 60 mcg/kg rFVIIa, a lower dosage than usually suggested, is efficacious in controlling massive bleeding in off-label use. Our data show that rFVIIa is haemostically active even at low fibrinogen levels. Additional data are required to confirm the beneficial effect of co-administering tranexamic acid.

Figure 1
Bleeding rate before and 30 min after rVIIa

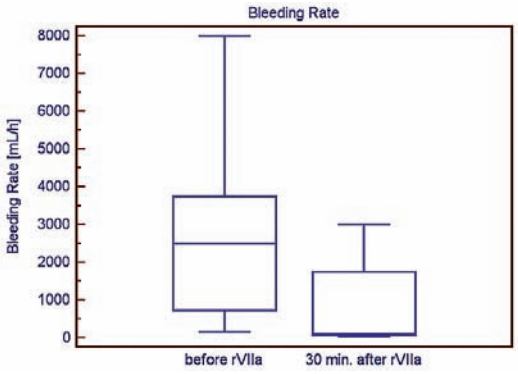
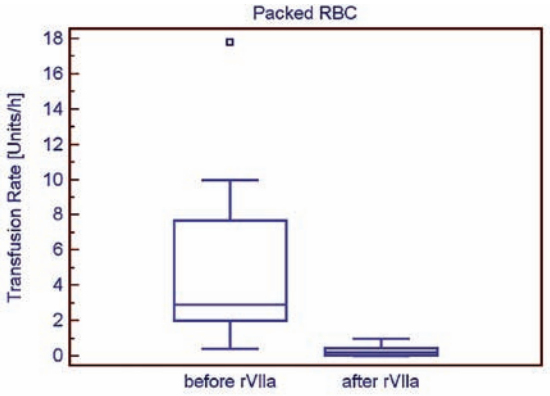


Figure 2
Packed RBC before and after rVIIa



P166

Recombinant human factor VIIa modulates endothelial thromboresistance in vitro

Madon J., Ruf W., Leikauf M.S., Valsami S., Fehr J., Asmis L.M. (Zürich, La Jolla)

Background: The hemostatic agent recombinant human FVIIa (rhFVIIa) when used at pharmacologic doses is believed to interact with TF on the surface of target cells such as activated platelets or subendothelial TF+ cells at sites of vascular injury. We hypothesize that in the presence of an inflammatory stimulus endothelial cells express functional TF, which may interact with rhFVIIa. It is the aim of our study to investigate functional TF expression in human endothelial cells in vitro in response to short and long term exposure to rhFVIIa in the presence of an inflammatory stimulus.
Materials and methods: Human umbilical vein endothelial cells (HUVEC) were incubated with pharmacologic concentrations of rhFVIIa (3 and 15 μg/ml) short term (1 hour) or long term (20 hours) in the absence or presence of TNFα (10–100 ng/ml). Tissue factor activity of adherent cells was analyzed using a FVII- and FX-dependent, commercial coagulation assay using a FXa-specific substrate. Tissue factor protein on the cell surface and in the whole cell were investigated by flow cytometry and Western blotting, respectively. TF gene expression was analyzed by real time PCR. A mixture of TF-specific antibodies that inhibit rhFVIIa binding was utilized to assess specificity.
Results: Basal expression of TF activity in HUVEC is at the limit of detectability. TNFα induced an approximately 10-fold increase in TF activity. rhVIIa induced a 15–30% reduction of TF activity in short-term and 40–50% in long-term experiments. A dose-response effect was observed in short-term but not in long-term experiments where both doses inhibited TF expression to a similar extent. The TNFα-induced increase of TF activity could be blocked by approximately 95% by antibodies known to block TF-rhFVIIa interaction.
Conclusions: In the presence of an inflammatory stimulus cultured endothelial cells in vitro express tissue factor activity that can be suppressed by specific antibodies. Pharmacologic doses of rhFVIIa reduce functional TF activity thereby modulating endothelial thromboresistance. The mechanisms underlying this effect are under current investigation.

P167

Transfusion efficacy of ABO major-mismatched platelets in children is inferior to ABO-identical platelets

Julmy F., Ammann R.A., Mansouri Taleghani B., Fontana S., Hirt A., Leibundgut K. (Bern)

Background: In contrast to transfusion of red blood cells, where ABO-major compatibility is mandatory, this is not the case for platelets.
Patients and methods: In a prospective study in thrombocytopenic children we investigated the impact of providing either ABO-identical or out-of-group single donor apheresis platelet concentrates (APCs) by measuring the 1-hour percent platelet recovery (PPR1h). We intended to prove the hypothesis, that there is a significant difference in transfusion efficacy comparing ABO blood group identical with ABO major-mismatched platelet transfusions. 400 APCs (median, 5/child, range, 1–68) were transfused to 50 children (29 girls, age 0.2–16.1 y). In case of major-mismatched transfusions from group A donors, A antigen expression on platelet surface was measured by flow cytometry in both the APC and in the recipient before and 1 hour after transfusion. Linear mixed effect (LME) modeling was applied for univariate and multivariate analyses. This parametrical method accounts for the correlation among transfusions given to the same patient.
Results: Transfusion efficacy of ABO major-mismatched APCs was significantly inferior to ABO identical platelets as shown by univariate LME analysis in table 1. Although transfusion efficacy was significantly influenced by other APC-related variables, major-mismatched transfusions remained significantly inferior to identical ones also by multivariate LME analysis (table 2). In case of major-mismatched transfusions from A1 donors expressing A antigen on their platelets, we showed by flow cytometry and fluorescent microscopy a rapid clearance of these platelets from the circulation in group O and B recipients. After major-mismatched transfusions of A2 platelets, expressing no detectable A-antigen, and also after minor-mismatched transfusions, the PPR1h did not differ from ABO-identical transfusions (median 36%, $P = .58$, and median 34%, $P = .69$, respectively).

Conclusions: Major-mismatched platelet transfusions were significantly less efficient than ABO-identical transfusions. In children requiring regular and continued platelet support, an ABO compatible transfusion strategy should be the choice. In this context, transfusion of major-mismatched A2 platelets was equivalent efficient as ABO-identical APCs, and this was also the case for minor-mismatched (plasma incompatible) APCs, but in the latter there remains an inherent risk for hemolytic transfusion reactions.

Table 1. Univariate linear mixed effect analysis of platelet transfusion efficacy depending on ABO-matching

Platelet Transfusions	n	PPR_{1h}		p
		Median	IQR*	univariate LME
Total	**400**	**31%**	**17% - 45%**	
ABO identical	**282**	**32%**	**19% - 44%**	**reference**
ABO major-mismatched	**76**	**21%**	**12% - 40%**	**0.035**
major-mismatched A_1	49	18%	13% - 34%	0.003
major-mismatched A_2	17	36%	17% - 52%	0.58
major-mismatched non A_2	57	18%	10% - 37%	0.004
ABO minor-mismatched	**42**	**34%**	**16% - 52%**	**0.69**
ABO non identical	**118**	**26%**	**14% - 45%**	**0.14**

*IQR = Interquartile range

Table 1

Table 2. Multivariate linear mixed effect analysis of ABO-matching- and product related factors affecting transfusion efficacy

Variable	n	PPR_{1h} Estimate	95%CI	p
ABO-matching related				
ABO major-mismatched vs. identical		**-2.45**	**-4.56 to -0.34**	**0.038**
Product related				
Apheresis and storage procedure: Amicus vs. others		-8.10	-9.99 to -6.21	<0.001
Storage time of APC [per day]		-4.47	-5.85 to -3.10	<0.001
Volume of APC [per mL]		0.14	0.10 to 0.18	<0.001
Gamma irradiation		-3.98	-6.40 to -1.57	<0.001

Table 2

P168

WBC reduction of blood products may be associated with a decreased incidence of allominunization

Koeppel R., Schanz U., Stussi G. (Zürich)

Alloimmunization to red blood cell (RBC) antigens is a common and potentially serious clinical problem. It has been hypothesized that white blood cell (WBC) reduction of blood products may reduce the number of alloimmunizations. Therefore, we retrospectively analyzed the the incidence of RBC antibodies (Ab) in the University hospital Zürich over the last 33 years (1973–2006). RBC Ab were detected by a 2 or 3 cell panel antibody screens (AS) and positive results were further specified by additional RBC panels. During this time, a total of 378'785 AS were performed and 4097 patients had 5340 positive AS (1.4%). The median age of the patients was 43 years (range 0–100) and 66% were female. Antibodies were most commonly directed against Rhesus (45%), Lewis (18%), and Kell (16%). The frequency against Duffy, Kidd, Lutheran, MNS, and P blood group system was below 10%. The most common Ab were anti-E (17%), anti-D (16%), anti-K (16%), and anti-Le^a (12%). Of the alloimmunized patients, 86% had 1, 12% had 2 and 2% had 3 Ab. One patient had 10 alloantibodies. Females were more likely to have Ab against Rhesus and males against Kell, Duffy, Lutheran, and P1. Since 1990, the number of positive tests was increasing with a maximal incidence of 4.3%. However, after 1999 the incidence of positive AS has decreased rapidly to 1% coinciding with the introduction of general WBC reduction.

P169

Erythrocyte storage in hypertonic (SAGM) or isotonic (PAGGSM) conservation medium: Influence on cell properties

Zehnder L., Schulzki Th., Goede J.S., Hayes J., Reinhart W.H. (Chur, Zürich, Davos)

Background and objectives: Red blood cell (RBC) storage for transfusion purposes leads to a time-dependent deterioration of cell properties (storage lesions). The aim of this study was to analyse the role of either a hypertonic or isotonic additive preservation solution on such parameters.
Materials and methods: RBC units were prepared from 20 blood donors using either saline-adenin-glucose-mannitol (SAGM; 376 mosm/l) or phosphate-adenin-glucose-guanosin-saline-mannitol (PAGGSM; 285 mosm/l) as an additive solution. At the beginning (days 0–2) and the end (days 42–44) of storage at 4 °C, RBC properties were studied. The mean cellular volume (MCV) was calculated from the microhematocrit, morphology was assessed on fixed RBCs, aggregability was tested by the sedimentation rate (ESR) in 3% dextran 70, osmotic dependant RBC deformability by ektacytometry, and RBC suspension viscosity with a Couette viscometer (Contraves LS-30).
Results: The MCV, measured in the native suspension by microhematocrit, increased from 87.6 ± 3.1 fl to 100.7 ± 4.3 fl in PAGGSM and to 92.2 ± 2.5 fl in SAGM ($p < 0.001$), after 42 days it was 95.8 ± 4.0 fl and 93.8 ± 3.9 fl, respectively. For both additives similar echinocytic RBC shape transformations were observed after storage, and aggregability was decreased (ESR 44 ± 22 and 25 ± 17 mm/2h, $p = 0.001$). Spontaneous hemolysis and osmotic fragility were less after storage in PAGGSM than in SAGM. Ektacytometry showed a slight decrease of osmotic dependant RBC deformability for both additives. After storage, the viscosity of RBC units (Hct 61 ± 3%) and resuspensions of RBC in fresh plasma (Hct 42 ± 2%) increased similarly.
Conclusions: The isotonic additive solution PAGGSM induced more RBC swelling in the beginning and decreased spontaneous hemolysis rate and osmotic fragility at the end of a 42-days storage than hypertonic SAGM. All other parameters such as echinocytosis, decreased RBC deformability and aggregability and increased blood viscosity were similar for both additive solutions and remain a major problem of blood banking.

P170

Globale Thrombusfestigkeit in vitro (Thromboelastometrie) als Transfusionstrigger für die Thrombozytentransfusion bei Patienten in Aplasie?

Schreiber A., Arber C., Buser A., Stern M., Marbet G.A., Gratwohl A., Tsakiris D.A. (Basel)

Thrombopenie ist eine obligate Nebenwirkung intensiver Chemotherapie. Zur Vorbeugung von Blutungskomplikationen werden bei aplastischen Patienten prophylaktische Thrombozytentransfusionen verabreicht. Der Richtwert für die Transfusionsindikation (5, 10 oder 20 G/L), sog. «Transfusionstrigger», ist immer noch Diskussionspunkt. Zusätzliche Begleitfaktoren (Fieber, DIC, u.a.) werden dabei arbiträr berücksichtigt. Ein besserer Test als die Thrombozytenzahl wäre wertvoll. Die Thromboelastometrie – eine Methode zur Evaluation der globalen Hämostase im Vollblut – wird als möglicher Test diskutiert. Wir untersuchten, ob sie sensitiv genug ist, Veränderungen vor und nach prophylaktischen Thrombozytentransfusionen zu erfassen.
Methoden: Thromboelastometrie (RoTEM) wurde im Citrat-Vollblut (0,11M, 1:9 v/v) vor und 1h nach Transfusion eines Einzelspender-Thrombozytenkonzentrats bei 23 Patienten nach Stammzelltransplantation evaluiert (Alter 51 ± 15, 6F, 17M). Der Tranfusionseffekt wurde mittels des "corrected count increment, CCI" nach 1h bewertet. CFT (clot forming time) und MCF (maximal clot formation) wurden nach Stimulation mit einem Phospholipid-Reagens für die extrinsische (ex) oder intrinsische (in) Gerinnung erfasst. Zusätzlich wurde die prokoagulatorische Mikropartikelaktivität als Thrombingenerierung im Plasma bestimmt (Zymuphen-Test).
Resultate: CFTex als Ausdruck schnellerer hämostatischer Reaktion wird im individuellen Patienten signifikant kürzer unmittelbar nach Transfusion (299 ± 217 vs 185 ± 120 s, $p < 0,001$). MCFex, als Ausdruck maximaler Gerinnselbildung steigt ebenfalls signifikant an (34 ± 7 vs 43 ± 6 mm, $p < 0,001$). CFTin und MCFin verändern sich in der gleichen Richtung. Die Veränderung am MCF bleibt sowohl bei adäquatem (>7,5) wie auch bei ungenügendem CCI (<7,5) signifikant, wobei stärker bei gutem CCI. Delta_MCF aber nicht Delta_CFT korreliert signifikant mit CCI (Rho = 0,64, $p < 0,01$). Die Mikropartikelaktivität im Plasma hat sich nach der Transfusion durchschnittlich um 47% erhöht ($p < 0,01$), statistisch signifikant nur beim hohen CCI (vor 5 ± 8 nM, nach 9 ± 10 nM, $p = 0,01$).
Schlussfolgerung: Diese Daten zeigen, dass die in vitro Thrombusfestigkeit mit der Thrombozytenzahl und dem CCI korreliert. Dies dient als Ausgangsbasis den Wert der Thromboelastometrie als Transfusionstrigger für die Thrombozytentransfusion in klinischen Studien zu untersuchen.

P171

Social Background and Delirium Syndrome as early markers of prolonged hospital stays in older inpatients with dementia

Lang P.O., Hermann F.R. (Genève)

Objectives: To identify early markers of prolonged hospital stays in elderly patients with dementia in acute hospitals.
Design: A prospective and multicentre study (9 hospitals in France).
Particpants: 468 medical inpatients with dementia at baseline and hospitalized through an emergency department were considered.
Method: Data used in a logistic regression were obtained through a CGA conducted in the first week of hospitalization. The center effect was considered as a random effect. Prolonged hospital stay was defined with a threshold adjusted for DRG according to the French classification.
Results: Two-thirds of subjects in the cohort analyzed were women, with a mean age of 86. Over 65% of subjects lived at home and 75% reported that they had a caregiver. Formal and informal caregivers were presents whatever the dependency level observed. Of the informal caregivers interviewed, 77% declared to feel severe burden. Thirty-one stays (7%) were prolonged beyond the f-DRG-adjusted limit. No demographic variables seemed to influence the length of stay. In multifactorial analysis, a diagnosis of delirium syndrome in the first week of hospitalization (odds ratio (OR) = 1.81) was identified as an early marker of prolonged hospital stays. In addition, social background data seemed to have a predictive value. The disclosure of a severe burden according to the Zarit's Burden Inventory (OR = 1.24) and, a bad social life in informal caregivers (OR = 0.92), corresponding with social score of the Duke's Health Profile, were likewise associated with prolonged stays. Dependence and cognitive impairment levels were not identified as risk factors.
Conclusion: The observed results suggest that, in a preventive approach of prolonged hospital stays, interventions of multidisciplinary networks are needed. Already, before hospitalization, home health care programs aimed at detecting crisis factors and establishing early prevention of crisis states may improve unfavourable medical and social condition and reduce unplanned hospitalization. In hospital setting, a specialized ward dedicated to demented patients with somatic diseases where management of BPSD and/or delirium is delivered by cooperating geriatrician and psychiatrist in association with an early social and psychological support appears to be an interesting preventive approach to avoid prolonged hospital stays in this population.

P172

Barriers to and facilitators of colorectal cancer screening in the elderly: a systematic review

Guessous I., Dash C. (Lausanne, Atlanta)

Background: Although there have been many studies evaluating factors related to CRC screening, little is known about the barriers to, and facilitators of, CRC screening participation among the elderly.
Methods: We conducted a systematic literature search in Medline (1995 to March 2007) and scanned reference lists of reviews to identify studies that reported barriers to or facilitators of CRC screening uptake, compliance or adherence specifically for the elderly population (65 and older). We extracted information on study interventions, baseline characteristics, and assessed whether barriers and facilitators were related to subjects, healthcare provider, policy or screening tests.
Results: 74 studies met the eligibility criteria. The majority (65/74) reported subject specific barriers/facilitators, 17 reported barriers/facilitators related to healthcare providers, 26 reported policy barriers/facilitators, and six reported screening test specific barriers. Low level of education (13/65 citations), black race (9/65), low socioeconomic status (9/65), female gender (8/65), and lack of insurance (8/65) were the most frequently reported barriers related to elderly. Twelve studies reported co-morbidities and perceived health status as "good" as barriers to CRC screening in the elderly. Being married or living with partner was the most frequently reported facilitators related to elderly (8/65). Having a family history of CRC and a positive attitude towards screening were also reported as facilitators. Most cited barriers related to healthcare provider were physician recommends/believes in stopping screening at a certain age (9/17) and lack of screening recommendation by physician (8/17). Physician's beliefs about whether screening is beneficial, higher proportion of primary care providers in county (vs. specialists) were reported as barriers as well. Lack of health care insurance coverage (8/26), rural residence (5/26), and dual coverage with Medicare and Medicaid (3/26) were the most frequent reported barriers related to finances, access and policy, whereas 2001 Medicare coverage of colonoscopy (5/26) and having a usual source of care (5/26) were consistently reported as a facilitators.
Conclusions: Numerous subject, healthcare provider, policy and test specific barriers to and facilitators of CRC screening in the elderly were identified. They might be used to better tailor interventions to increase CRC screening participation rates in the elderly.

P173

Stratégies pour bien vieillir. Le défi gérontagogique

Rapin C.H., Ruchat M. (Sion et Genève, Genève)

A l'ensemble des défis contemporains qu'entraîne l'allongement de l'espérance de vie en bonne santé, les auteurs proposent d'ajouter le «pari gérontagogique». Les concepts du «Bien vieillir» et de «Value based medicine» (Rapin, 1999) se voient ici prolongés par celui de «gérontagogie» définit comme l'art de bien conduire sa vieillesse. Sous ce néologisme, les auteurs exposent leur hypothèse de la formation des aînées et des aînés comme un déterminant de bonne santé. Ils s'appuient sur l'expérience d'un programme original de formation transdisciplinaire, alliant notamment sciences médicales et sciences de l'éducation. Cette formation nouvelle possède trois caractéristiques essentielles: 1/ le travail en synergie des étudiantes et étudiants de plusieurs générations, 2/ la recherche de solutions aux problèmes de la vieillesse (solitude, manque d'autonomie, douleur, maltraitance, etc.) dans le respect des valeurs de tous les acteurs du champ du vieillissement, et 3/le changement dans les représentations et les pratiques sociales opéré par la formation. Cette formation certificative est une des formes de l'«empowerment» faisant partie des stratégies pour «Bien vieillir».

P174

Residents' difficulties vis-à-vis end-of-life care

Luthy C., Cedraschi C., Pautex S., Rentsch D., Piguet V., Allaz A.F. (Geneva)

Background: Residents in training are first-line physicians in hospital settings and they are in the process of developing knowledge and mastering clinical skills. They have to confront complex tasks calling upon their personal background, their professional identity, their relationships with the patients, and with the members of the multidisciplinary team.
Objective: In order to improve the clinical guidance of residents faced with terminally ill hospitalized patients, we investigated the difficulties perceived by internal medicine residents in end-of-life care.
Methods: 24 consecutive first-year residents in internal medicine were presented with the following question in a written form: "In your experience, what are the difficulties and concerns you identify in the management of a terminally ill patient hospitalised for end-of-life care?". A qualitative procedure was applied. The answers were submitted to content analysis performed by three independent researchers. Inter-rater agreement was high (kappa coefficient = 0.88); disagreements were solved by consensus.
Results: Physicians' characteristics: female 37%; mean age 28 ± 2.2 years, mean duration of postgraduate training 2.5 ± 1.3 years. Total number of answers: 82; the average number of responses/resident was 3.3 ± 1.3. As 31 out of 82 answers included more than one category of difficulties/concerns regrouped into the same sentence, they were split for analysis, yielding a total of 114 analyzed items. Eight categories were obtained, encompassing the difficulties/concerns expressed by the residents: provide adequate explanations; face one's limits/the limitations of medicine; decipher the queries; avoid flight; manage provision of time; have sufficient theoretical knowledge; avoid false reassurance; and be able to help in spite of everything.
Conclusions: These results stress that residents identify the complexity of the dimensions of care in terminally ill patients early or very early in their training. These junior residents' responses point to the right distance in-between getting involved and preserving oneself as a dimension of major importance. Issues related to proximity with the patient facing a terminal illness seem to be (at least) two-sided, in-between avoidance or even flight – too far – and bonding or fusion – too close.

P175

Lutter contre la sous-notification des effets indésirables cutanés en gériatrie: un projet de pharmacovigilance proactive

Villaneau D., Trellu L., Plachta O., Vogt-Ferrier N. (Genève, Swissmedic-Berne)

La pharmacovigilance suisse repose sur la notification spontanée des effets indésirables médicamenteux à Swissmedic*. Postulant une sous-notification des réactions cutanées induites par les médicaments (toxidermies) en gériatrie, nous avons instauré en 2007 une recherche active des cas survenant dans un hôpital universitaire de soins gériatriques aigus. De fait, en 2007, 60% des 50 déclarations de pharmacovigilance provenant de cet hôpital ont concerné des toxidermies.
Bilan: 5 réactions SEVERES: – 2 DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Imputés: cyanocobalamine/picosulfate; clopidogrel
– 2 érythèmes polymorphes, un buccal stoppé à un stade débutant (polymédication), un périorbitaire lisinopril/métoprolol/penicilline G/norfloxacine
– possible Pustulose Exanthématique Aiguë Généralisée (PEAG) amoxicilline/ac.clavulanique)
Aucun érythème polymorphe majeur, ou Nécrolyse Epidermique Toxique (NET) de type syndrome de Stevens-Johnson (SJS) ou Lyell n'ont été signalés.
14 réactions BENIGNES:
– 11 exanthèmes maculo-papuleux allergiques. Imputés: antibiotiques 5/11
– 2 urticaires. Imputés: galantamine/picosulfate; gabapentine/galantamine
– 1 érythème pigmenté fixe: oxycodone
10 AUTRES types de réactions:
– 1 phototoxicité: co-trimoxazole
– 4 vasculites leucocytoclasiques confirmées par biopsie (purpura vasculaire). Imputés: losartan/amoxicilline/enoxaparine; spironolactone; torasémide/fluoxétine/esoméprazole/enoxaparine; co-trimoxazole
– 2 prurits simples. Imputés: buprénorphine; tamoxifène
– 1 érythrodermie fugace sous répaglinide/digoxine
– 2 importants hématomes aux sites d'injection d'enoxaparine
– 1 dermite de contact à un patch de fentanyl
Discussion: 87% des lettres de sortie mentionnaient ces évènements cutanés ainsi que les médicaments imputés, témoignant d'une bonne documentation des réactions en fin d'hospitalisation. Par contre, au cours de leur séjour deux patients ont été réexposés (un lors d'un transfert) aux molécules imputées lors de la 1ere toxidermie. Ceci souligne la rigueur nécessaire dans le dossier patient pour de tels évènements.
Conclusion: Une recherche active des cas de toxidermie en gériatrie permet de lutter contre la banalisation de cette iatrogénie. La documentation immédiate des incidents dans le dossier de prescription permettrait d'éviter des ré-expositions accidentelles.
* Swissmedic, Institut suisse des produits thérapeutiques.

P176

Prevention of adverse drug reactions in a geriatric nursing home

Penasa U., Jäger M., Lutters M. (Baden)

Introduction: Older patients are more prone to adverse drug reactions than younger people because of polypharmacy, multimorbidities, renal dysfunction and increased sensitivity to side effects. Underlying diseases like dementia or depression make diagnosis of adverse drug reaction difficult.
Objectives: – prevent and detect medication related problems in a nursing home, – in details: develop a table on relevant adverse drug reactions of all drugs used in the nursing home including recommendations for control of laboratory parameters.
Methods: We focussed our research on cardiovascular, psychiatric and respiratory drugs used in the nursing home. Relevant side effects, recommended control parameters and pharmacokinetic data (Q_0, V_d, $t_{1/2}$) were searched in the following manuals respectively internet sites: – Arzneimittelkompendium der Schweiz 2007, – www.dosing.de, – Berthold H. Klinikleitfaden Arzneimitteltherapie 1999, Gustav Fischer Verlag Stuttgart, – Therapie-Profile für die Kitteltasche 2003, WVG Stuttgart. Based on these data we created a table with relevant and frequent adverse drug reactions and recommendations for monitoring of side effects, especially laboratory parameters.
Results/Discussion: Drugs eliminated mainly by the kidneys (Q_0 <0.5) were marked. Interactions were not considered because there are so many and they don't fit in a table.Instead, we provided a table with substrates, inductor and inhibitors of cytochrome P450. Information on frequency of laboratory controls was sparse, as well as information on monitoring of rare but serious side effects like hepatitis. Most drugs require a careful dose titration, for example beta blockers, antidepressants, antipsychotic, antiepileptic, and anti-Parkinson drugs.
Conclusion: Many adverse drug reactions in elderly patients may be avoided or early detected by carefully dosing, consideration of the kidney function and regularly monitoring of known side effects.

P177

Prévalence, sévérité et étiologie des troubles cognitifs en EMS

Joray S., Bourquin I., Ebbing K. (Lausanne)

Il existe peu de données épidémiologiques sur les troubles cognitifs et les démences au sein de populations vivant en EMS (Etablissement Médico-Social). Selon notre expérience de médecins gériatre et psychogériatre travaillant en EMS, les pathologies démentielles sont extrêmement fréquentes et représentent le premier motif d'institutionnalisation.
Objectifs: évaluer au sein d'une population vivant en EMS, la prévalence des troubles cognitifs, leur sévérité et leur étiologie, ce de manière systématique et sur une durée de 6 mois.
Population et méthodes: les personnes vivant dans un EMS de 79 lits gériatriques en ville de Lausanne ont été évaluées par un examen clinique ciblé, comprenant un status neurologique, un status mental ainsi qu'une évaluation psychiatrique lors d'antécédents psychiatriques. Une neuropsychologue a administré un MMSE (Mini Mental Sate Examination) à chacun des résidents et établi une échelle CDR (Clinical Dementia Rating) en fonction d'informations recueillies auprès du personnel soignant. Tous les documents médicaux antérieurs en relation avec une problématique cognitive ont été recherchés, notamment les examens neuropsychologiques et neuroradiologiques. Sur la base de l'évaluation clinique et des examens complémentaires, un diagnostic a été posé.
Résultats: au total 82 résidents ont été évalués sur une période de 6 mois. Leur âge moyen était de 85,8 ± 8,3 ans avec 78% de femmes. Le score MMSE moyen était de 12,7 ± 8,4. Plus de la moitié (n = 43) présentait une démence sévère CDR 3, 13,4% (n = 11) une démence modérée CDR 2 et 26,8% (n = 22) une démence légère CDR 1. Parmi les 6 personnes avec un CDR à 0.5, seules 2 (2,4%) étaient considérées sans trouble cognitif. Le diagnostic le plus fréquent est celui de probable maladie d'Alzheimer (n = 49, 59,6%), suivi des démences vasculaires et mixtes (n = 14, 17,0%), des syndromes Parkinson-démences, puis des étiologies psychiatriques, alcooliques et finalement des causes rares.
Conclusion: sur l'ensemble d'une population vivant en long séjour gériatrique, la presque totalité présente des troubles cognitifs. Pour la plupart, un diagnostic de pathologie démentielle a été retenu, de stade avancé dans la moitié des cas, le plus souvent une maladie d'Alzheimer. Les démences de par leur fréquence et leur impact fonctionnel sévère sont certainement le principal motif d'admission en EMS.

P178

Rôle du médicament dans les admissions aux soins intensifs

Besson M., Segala S., Chabert J., Piguet V., Chevrolet J.C., Dayer P., Desmeules J. (Genève)

Contexte: les effets indésirables médicamenteux (EIM) représentent jusqu'à 6% des admissions hospitalières et sont évitables dans les 2/3 des cas. On ne dispose que d'une littérature ancienne et peu étayée sur leur rôle dans les admissions aux soins intensifs (SI).
But: évaluer la part des EIM dans l'admission aux SI et leur caractère évitable.
Méthode: étude pilote, prospective. Pendant 1 mois, les jours ouvrables, les admissions dans le service des SI aux Hôpitaux Universitaires de Genève ont été analysées. Les motifs de transferts, les données démographiques, médicales et médicamenteuses ont été recueillies systématiquement. L'imputabilité de l'EIM dans l'admission aux SI a été posée par une pharmacologue clinique. Celle-ci déterminait également le degré d'évitabilité.
Résultats: 174 admissions (2/3 des admissions totales) ont été analysées, sur lesquelles on dénombre 111 hommes (64%) et 101 patients (58%) de plus de 65 ans. Les patients provenaient de la communauté (n = 102), des unités de soins (n = 32) et du post-opératoire (n = 34). Les EIM ont joué un rôle dans 20% des admissions (34/174). 3 des ces 34 cas (9%) était des tentamen, dont l'imputabilité médicamenteuse était certaine. L'imputabilité de l'EIM était probable dans 20% des cas (7/34) et ces EIM évitables dans 40% des cas (3/7). Pour les 18 cas restant (70%), l'imputabilité était possible. Les principaux effets indésirables étaient cardiovasculaires et hémorragiques. Les médicaments les plus fréquemment en cause étaient les [beta]-bloquants, les antiaggrégants plaquettaires et les corticoïdes. La polymédication (>3 médicaments), l'insuffisance rénale (Clcréat <50 ml/min) et le sexe féminin sont retrouvés comme facteurs de risque d'être admis aux SI pour un EIM.
Conclusion: les EIM représentent une cause importante d'admission aux SI et une partie d'entre eux sont évitables. Une étude de plus grande envergure, avec évaluateurs indépendant, devrait permettre de confirmer ces résultats, de préciser le coût humain mais aussi financier de ces EIM et pour ceux qui sont évitables d'envisager des stratégies de prévention.

P179

The characteristics and relationship between the effect size and the odds ratio

Curtin F., Schulz P. (Genève)

Background: In clinical trials and meta-analyses, the status of responder or non-responder to a treatment is generally derived from a clinical variable measuring efficacy on a continuous scale. In trials and meta-analyses, the measurement expressed on a continuous scale is often evaluated by the effect size (difference of means divided by a standard deviation), whereas the binary variable corresponding to the responder status is assessed by the odds ratio (OR).
Objective: The relationships between the effects size for continuous outcome and the measure of association for the derived binary variables, the OR, are analysed.
Results: The mathematics describing the statistical metrics, OR and effect size, are presented and their mathematical relationship is analysed. The cut-off point on the continuous scale which determines the responder status plays a role in the mathematical relationship between OR and effect size. The impact of the location of the cut-off point on the continuous scale is analysed: the location of the cut-off point vis-à-vis the distributions of the continuous variables corresponding to the experimental and control treatments is essential. According to the location of the cut-off point, the OR can be maximised. The OR is maximal if the cut-off is located at a point equidistant from the means of the two distributions of the variables representing experimental and control treatments outcomes. The dependence of the OR on the magnitude of the effect size as well as on the location of the cut-off point has important consequences on the analysis of results of clinical trials: by changing the definition of responders, i.e. by changing the location of the cut-off point, one can obtain different results in terms of OR.
Conclusion: The responder status must be defined before the results of the trial are analysed and, to ensure transparency, the results obtained in treatments groups measured on the continuous scale must be presented along the results obtained with the binary variable responder/non-responder.

P180

Amélioration continue de la prescription en gériatrie

Vogt-Ferrier N., Parel Y., Villaneau D., Allali D., Gschwind L., Bouchoud Bertholet L., Ciubotariu M., Dayer P. (Genève)

Introduction: Les médicaments sont souvent source d'incidents indésirables médicamenteux (IIM): effets indésirables, interactions néfastes et problèmes liés à la prise en dehors des circonstances prévues pour leur usage.
Objectif: Créer un outil d'assurance qualité pour identifier et quantifier les IIM. Fournir une image dynamique de la qualité de la prescription dans un hôpital gériatrique universitaire de soins aigus et définir des priorités d'amélioration.
Méthode: La méthode, adaptée de protocoles éprouvés [1, 2], repose sur une revue rétrospective d'un échantillon aléatoire de dossiers patients. On y recherche différents indicateurs, dont la présence engendre une analyse plus fine afin d'identifier des IIM, un non-respect de recommandations de prescription ou d'administration.
Résultats: N = 50 dossiers, soit 11'811 doses de médicaments. 121 indicateurs d'IMM ont été détectés dont 78 (0,66 pour cent doses de médicaments) étaient liés à un IIM (augmentation de la créatininémie (15,4%), somnolence (10,3%)). Parmi les critères de non-conformité, 53 indicateurs ont été détectés dont 38 (0,32 %) étaient des prescriptions non conformes aux recommandations (IPP sans réelle nécessité (42,1%)). Parmi les 43 indicateurs liés à l'administration détectés, 4 (0,03%) médicaments étaient utilisés sans respecter les modalités d'administration (antibiotique iv alors que per os possible [100%]).
Discussion: L'analyse confirme la fréquente iatrogénie décrite en gériatrie (3). Le nombre d'IIM relevé dans notre étude (0.66%) est plus élevé que dans une autre étude similaire (0,2%) (4). Le protocole a été modifié afin d'affiner les critères concernant l'insuffisance rénale aiguë. Certains critères américains (2), avérés peu pertinents, ont été remplacés.
Conclusion: Dynamique et modulable, cet outil peut s'adapter à tout environnement, est facile d'emploi et permet une surveillance qualité continue. Il procure de précieuses indications sur les mesures d'amélioration à implémenter pour éviter les pratiques de prescription risquées.
Références: 1. Griffin, FA, Resar RK. IHI Global Trigger Tool for Measuring Adverse Events. 2007 (disponible sur www.IHI.org) 2. Fick DM, et al, Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Arch Intern Med 2003; 163:2716-2724 3. Bases de la thérapeutique médicamenteuse, 16e éd., 2005, 274–277. 4. Cohen MM, and al. J Qual Saf Health Care. 2005 Jun;14(3):169–74.

P181

Assessment of potential drug-drug interactions at hospital discharge

Bertoli R., Caronzolo D., Bissig M., Waldispühl B., Lozano Becerra J.C., Odorico M., Pons M., Bernasconi E. (Lugano, Bellinzona)

Background: About 5% of all adverse drug reactions in hospitals are caused by drug-drug interactions, the majority of which are avoidable. Up to 10% of all hospitalized patients have at least one adverse drug reaction after discharge. Change of medication during hospital stay and lack of therapeutic care after discharge are among the most important risk factors for drug related problems. For the patients it is therefore of great importance that discharge medication has the lowest risk of potential drug-drug interactions and that doctors are aware of possible, preventable, drug-related complications.
Aim: Evaluation of the prevalence of potential drug-drug interactions and assessment of their clinical relevance in patient's discharge medication in the medical ward of a community teaching hospital. The clinically relevant information was reported to the treating physicians.
Methods: Prospective study of medication from 51 patients (200 at the end of the study) at discharge from a medical ward. Prescribed drugs were analysed for interactions using a commercially available software (Pharmavista®). Two clinical pharmacists and a physician assessed the clinical relevance of detected interactions, eliminated those which were considered clinically not relevant and elaborated recommendations for those considered clinically relevant.
Results: The mean age of the 51 patients studied so far (19 men, 32 women) was 68 years. At discharge, patients took an average of 7 different drugs. 67% of patients had at least one potential drug-drug interaction. In total, 105 potential drug-drug interactions were

identified: 62 (59%) of minor severity, 34 (32%) of moderate severity and 4 (4%) of major severity. Oral anticoagulation and acetylsalicylic acid were the most frequently implicated drugs. 66% of the overall detected interactions were considered clinical relevant and resulted in a warning to the treating physician.
Conclusions: A computerised drug-drug interaction programme (detection) together with clinical pharmacological experience (interpretation/evaluation) can be useful for decreasing the number of potential harmful drug combinations. This approach may lead to an improvement in the quality of prescription, preventing possible risks and thus contributing to the patient's safety.

P182

Tödliche Intoxikation mit Eibennadeln (Taxus baccata) bei einer 44-jährigen Patientin

Berthold P., Mattes H., Stürer A., Neuhaus M., Plattner T., Brunner H.R., Beer H.J. (Baden, Zürich, Bern)

Hintergrund: Seit dem Altertum wird die Eibe zu Mord, Selbstmord und Abtreibung missbraucht. Als immergrüner Nadelbaum wächst die Eibe langsam, wird bis 1000 Jahre alt und 15 m hoch. Nadeln, Rinde und Samen sind stark giftig, die roten Früchte nicht. Sie enthält ein Alkaloidgemisch: Taxin B (30–40%), Taxin A (1,3%), Taxol, Biflavonoide und cyanogene Glycoside. *Taxin B* ist kardiotoxisch, hemmt den Na- und Ca-Transport in die Myokardzellen. Niedrige Konzentrationen sind positiv ino- und chronotrop, höhere bewirken einen AV-Block bis zur Asystolie. *Taxin A* ist auch hochdosiert bradykardisierend. *Taxol* ist ein Mitosehemmer.
Fallbeschreibung: Eine 44-jährige Pat., wegen Depression in Psychiatrie hospitalisiert, nahm nach Selbststudium über Eibenintoxikationen im Internet eine Handvoll Eibennadeln in suizidaler Absicht ein. Nach 2 h traten Schwindel, Nausea/Vomitus und eine progrediente Bewusstseinstrübung sowie Kreislaufinstabilität auf, gefolgt von wechselnder Vigilanz, Sehstörungen und Hypotonie. Im EKG polymorphe Breitkomplextachykardien, rasch wechselnd mit extremer Bradykardie bis 20/Min. Nach Einlage einer Magensonde kam es erneut zu Bradykardie und Kammerflimmern, welches zunächst erfolgreich defibrilliert wurde. Nach Intubation, Gabe von Mg und Noradrenalin Kreislaufstabilisierung, die Pupillen waren mydriatisch und reaktionslos. Im Echo fand sich eine völlig asynchrone Herzaktion. Nach erfolgter Magenspülung trat erneut eine Bradykardie auf, gefolgt von einer Kammertachykardie, die trotz Defibrillation persistierte, in ein Kammerflimmern und dann in eine Asystolie überging, die auf externes und internes Pacing refraktär war. Die Reanimation wurde daraufhin (6½ h nach Eintritt) abgebrochen.
Diskussion: 50–100 g Eibennadeln gelten als tödlich. Nach Aufnahme zerkleinerter Eibennadeln treten Symptome wesentlich schneller auf. Wichtig ist die primäre Giftelimination (Aktivkohle, Magenspülung, evtl. Gastrokopie), eine spezifische Therapie ist nicht bekannt. Es wurden Fälle mit massiv erhöhtem Digitalisspiegel beschrieben (Kreuzreaktivität), anekdotisch war die Therapie mit Digitalis-spez. AK erfolgreich (der Digitalisspiegel unserer Pat. war <0,26 nmol/l). In einem weiteren Fall war eine Therapie mit Lidocain erfolgreich.
Schlussfolgerung: Die Eibenintoxikation verläuft leider auch heute noch meist tödlich, da eine spezifische Therapie nicht existiert und die Giftelimination oft zu spät kommt.

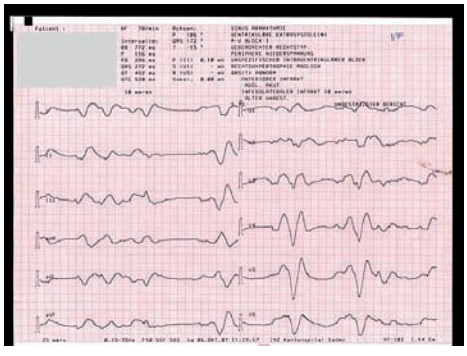


Abb. 1
EKG bei Eintritt

P183

Measurement of free plasma levels of antiretroviral drugs using a new ultrafiltration method circumventing the loss by adsorption reveals high interindividual variability in free fractions

Fayet A., Buclin T., Telenti A., Biollaz J., Decosterd L.A. (Lausanne)

Background: Total plasma levels are used for Therapeutic Drug Monitoring of antiretroviral drugs, whereas unbound concentrations are expected to exert antiviral activity. The determination of free drug levels in plasma can be performed by ultrafiltration, a technique flawed however by the irreversible adsorption of many drugs onto the membrane filters and plastic components. This results in spuriously low levels and underestimated free fractions. We report a new procedure for the accurate measurement of unbound plasma levels of antiretroviral drugs by ultrafiltration.
Methods: During in vitro experiments, plasma spiked with antiretroviral drugs were placed in pre-washed Centrifree ultrafiltration tubes, and centrifuged at 2000 g. The ultrafiltrate was collected in four fractions (0–8, 8–16, 16–24 and 24–30 minutes), diluted 1:1 with MeOH without delay, and analysed by LC-MS/MS.
Results: Free drug levels in the early 0-8 min ultrafiltrate fraction were very low and highly variable, and gave free fractions substantially lower than the mean value in the late three fractions (8–16,16–24 and 24–30 minutes) for lopinavir (mean: 0.89 vs 2.01%, $p < 0.01$), nelfinavir (0.091 vs 0.52%, $p < 0.01$), saquinavir (0.98 vs 2.73%, $p < 0.01$), tipranavir (0.014 vs 0.072%, $p < 0.01$) and efavirenz (0.28 vs 1.17%, $p < 0.01$). In the two last fractions, the ultrafiltrate levels remained constant, indicating a saturable initial drug adsorption without further influence on the accuracy of free drug level determination beyond 16 min of ultrafiltration. The adsorption phenomenon was modest for indinavir, amprenavir and ritonavir and unnoticeable for atazanavir and nevirapine. Applied to patients' plasma, the procedure reveals a substantial inter-individual variability in the free fraction for many antiretroviral drugs.
Conclusions: The change in procedure for the determination of free antiretroviral drug levels enables to circumvent drug loss due to early adsorption on ultrafiltration membrane. Measurement of free drug levels is thus made easier in special situations (pregnancy, haemodilution, protein level changes, liver/kidney insufficiency etc.).

P184

Low-dose Valganciclovir is efficacious and safe for prophylaxis of cytomegalovirus infection in kidney transplantation

Perrottet N., Manuel O., Venetz J.P., Lamoth F., Decosterd L.A., Buclin T., Biollaz J., Meylan P., Pascual P. (Lausanne, Edmonton)

Background: Optimal valganciclovir (VGC) dosage and duration for cytomegalovirus (CMV) prophylaxis in kidney transplant recipients remains controversial. This study aimed to determine GCV blood levels and efficacy/safety observed under low-dose oral VGC in kidney transplant recipients. Secondly, to quantify the variability of GCV blood levels, and its potential clinical impact.
Methods: In this prospective study, each patient at risk for CMV undergoing kidney transplantation received low-dose VGC (450 mg qd) prophylaxis for 3 months, unless GFR was below 40 mL/min, in which case the dose was adapted to 450 mg every other day. GCV levels, at trough (Ctrough) and at peak (C3h) were measured monthly and CMV viremia was assessed during and after prophylaxis using real time quantitative Polymerase Chain Reaction. Adverse effects were recorded on each GCV sampling. Patients were followed up to one year after transplantation.
Results: 38 kidney recipients (19 D+/R+, 11 D+/R-, 8 D-/R+) received 3-month VGC prophylaxis. Most patients (mean GFR of 59 mL/min) received 450 mg qd but the dose was reduced to 450 mg every other day in 6 patients with mean GFR of 22 mL/min. Average GCV C3h and Ctrough (regressed at 24 h or 48 h) were 3.9 mg/L (CV 33%, range: 1.3–8.2) and 0.4 mg/L (CV 111%, range 0.1–3.3). Population pharmacokinetic analysis showed a fair dispersion of the parameters mainly influenced by renal function. Despite this variability, patients remained aviremic during VGC prophylaxis. Neutropenia and thrombocytopenia (grade 2-4) were reported in 4% and 3% of patients respectively. During follow-up, asymptomatic CMV viremia was reported in 25% patients. One year after transplantation, 12% patients (all D+/R-) had developed a CMV disease, which was treated with a therapeutic 6-week course of oral VGC.

Conclusion: Average GCV blood levels after oral administration of low-dose VGC in kidney transplant recipients were comparable to those previously reported with oral GCV prophylaxis, efficacious and well tolerated. Thus, a 3-month course of low-dose VGC is appropriate for the renal function of most kidney transplant recipients.

P185

Disposition of oral valganciclovir during continuous renal replacement therapy in two lung transplant recipients

Perrottet N., Robatel C., Meylan P., Pascual P., Venetz J.P., Aubert J.D., Berger M., Decosterd L.A., Biollaz J., Buclin T. (Lausanne)

Background: Oral valganciclovir (VGC) is hydrolysed into active ganciclovir (GCV) which is eliminated in the kidney by filtration and secretion. VGC dosage has to be adapted in renal failure with continuous renal replacement therapy (CRRT), a condition sometimes encountered early after solid organ transplantation. This investigation aimed to determine whether VGC 450 mg every 48 hours provides appropriate GCV exposure for cytomegalovirus (CMV) prophylaxis during CRRT.
Methods: GCV pharmacokinetics were extensively studied during CRRT in two lung transplant recipients with acute renal failure receiving VGC 450 mg every 48 hours trough a nasogastric tube. In vitro experiments using blank whole blood spiked with GCV further investigated exchanges between plasma and erythrocytes.
Results: GCV disposition was characterised by an area under the curve (AUC) of 98.0 and 55.4 mg·h/L, resulting in trough concentrations of 0.7 and 0.2 mg/L, an apparent total body clearance of 3.3 and 5.8 L/h, a terminal half-life of 16.9 and 14.1 h, and an apparent volume of distribution of 60.3 and 104.9 L. The observed sieving coefficient (filtrate/plasma) was 1.05 and 0.96, and the hemofiltration clearance 3.3 and 3.1 L/h, respectively. High sieving values could be explained by an efflux of GCV from erythrocytes. In vitro experiments confirmed that erythrocytes are loaded with significant GCV amount and release it quickly into plasma, thus contributing to the apparent efficacy of hemofiltration.
Conclusion: These results indicate that a VGC dosage of 450 mg every 48 hours was adequate for CMV prophylaxis during CRRT, providing GCV levels similar to those reported using 900 mg qd in transplant recipients with normal renal function.

P186

Preliminary results: Topical retinoids during the first trimester of pregnancy

Panchaud A., Csajka C., Rousso Ph., Rothuizen L., Buclin Th., and the European Network of Teratogen Information Services E.N.T.I.S. (Lausanne, various places)

Background: While retinoids given orally are strong human teratogens, their topical use has not been formally prohibited during pregnancy, considering their very low absorption. However, isolated observations suggest a potential association with characteristic retinoid embryopathy. Epidemiological data are still scant to confidently confirm or rule out this risk.
Method: The Swiss Teratogen Information Service (STIS) carried out a collaborative observational study to evaluate the rate of congenital malformations following first trimester exposure to topical retinoids. Data prospectively recorded by the ENTIS members between 1992 and 2006 were collected using a standard questionnaire.
Results: Data were obtained on 248 pregnant women (age 30.5 ± 4.0, range 21–42) exposed to topical retinoids (11 lost to follow-up). 110/227 were known as primigravid, 136/226 as primiparous, 11/184 as reporting tobacco use, 23/174 alcohol use. 199 exposures occurred during the critical period for retinoid embryopathy (week 2 to 5) and 233 during the first trimester (mean week of call 10 ± 6, range 0–35). Exposures were to six different retinoids (adapalene 28, retinoic acid 12, tretinoin 148, isotretinoin 54, motretinide 1, tazaroten 1, combined 4). Congenital abnormalities were observed in 8 of 194 newborns known for first trimester exposure (prevalence 4.1%, CI95 1.3–6.9): congenital cerebral cysts with autism, bilateral polycystic kidneys with early termination, hemangiomas, angiomas, unilateral cataract, unilateral microphtalmia, cleft soft palate, and poly-malformation (ventricular septal defect, pulmonary valve stenosis, aorctic coarctation, undescended testes). Another 8 newborns presented minor variants: 2 ankyloglossia, 2 external ear misshape, hypermetropia, naevus, metatarsus varus. Further comparisons with a matched control group of unexposed pregnancies are underway.
Conclusions: The calculated confidence interval for the prevalence of abnormalities in this population encompasses the rate of anomalies (2–4%) reported in the general population. This study is sufficiently powered to exclude with fair certainty an effect of the order of a doubling or more of baseline risk. However, a small increase in congenital abnormalities cannot be ruled out. Concretely, these results bring reassuring elements in case of fortuitous exposure to topical retinoids. However, they can certainly not be recommended for use during pregnancy, as their risk/benefit ratio remains questionable.

P187

Delayed neurologic sequelae after acute carbon monoxide poisoning

Ruggieri F., Al-Haj Husain N., Kupferschmidt H., Joos B., Fischler M. (Zürich)

Case report: After being accidentally exposed to a residential fire for 30–40 minutes a 21-year-old woman was intubated because of coma and poor oxygen saturation (SaO2 80%). On admission she was mechanically ventilated with 100% O_2, the temperature was 37.4 °C, the heart rate 110/min, blood pressure 120/70 mm Hg and SaO_2 98%. The first arterial blood gas revealed: pH 7.1, pCO_2 6.3 kPa, pO_2 7.0 kPa, COHb 20%, O2Hb 64%, lactate 10.7 mmol/L. Troponine and ECG were normal. She then was transferred to the ICU. Hyperbaric oxygen (HBO) was not administered. After extubation on day 7 she progressively developed psychosis, parkinsonism, choreoathetosis in the upper limbs, mutism, central blindness, urinary and fecal incontinence suggesting delayed neurologic sequelae (DNS) secondary to carbon monoxide poisoning. MRI of the brain performed on day 14 revealed high-signal-intensity lesions on T2-weighted images in the caudate nucleus and putamen, posterior periventricular white matter and parieto-occipital cortex bilaterally, which showed gadolinum-enhancement on T1-weighted images. The lesions were consistent with encephalopathy by CO poisoning with bilateral striatal involvement and cortical laminar necrosis. She was started on amantadine 4 x 200 mg/d with improvement of her parkinsonism. She gradually regained neurological and neuropsychological function after 4 months rehabilitation.
Conclusion: Carbon monoxide binds to haemoglobin (COHb) with nearly 240 times the affinity of oxygen. Poisoning results mainly in cardiac and neurological damage. Delayed neuropsychiatric syndrome (DES) is characterized by amnesia, personality changes, movement disorders, focal deficits and develops in up to 40% of patients with significant CO exposure. It can occur insidiously days or even several weeks after apparent recovery and being discharged home (lucid intervals). The exact mechanisms by which CO produces these toxic effects are not yet well understood and the development of DNS correlates poorly with COHb levels. Pulse oximetry is unreliable because it overestimates SaO_2 in the presence of COHb. Mainstay of therapy remains 100% O_2 via high-flow mask and supportive care. Hyperbaric oxygen (HBO) accelerates dissociation of CO from hemoglobin and may prevent DNS, however the evidence is not convincing. The use of HBO should be considered in coma, cardiac dysfunction, severe acidosis (pH <7.1) and COHb >25% (in pregnancy >20%).

P188

In vitro study of P-glycoprotein interaction with naloxone and naltrexone

Kanaan M., Daali Y., Dayer P., Desmeules J. (Genève)

Background: The poor oral bioavailability of the opioid antagonist naloxone (NA) (<1%) as compared with that of naltrexone (NX) (up to 40%) seems to be related to a weaker intestinal absorption rate rather than a more extensive first pass metabolism. This could be attributed to a greater interaction of naloxone with the efflux drug transporter P-glycoprotein (P-gp) as compared with that of naltrexone.
Aim: We studied the involvement of P-gp in the transepithelial transport of the two opioid antagonists, using a human in vitro Caco-2 cell monolayers model.
Methods: Transmission electron microscopy (TEM), transepithelial electrical resistance (TEER), [^{3}H]-mannitol permeability, Western blot analysis and bidirectional transport of rhodamine 123 have been performed to assess the integrity of the Caco-2 model. The bidirectional transport of NA and NX (1, 10, 50 and 100 microM) across the

monolayers was investigated at physiological pH (7.4/7.4) in the presence and absence of the specific P-gP inhibitor elacridar (GF1210918) (4 microM). Analytical quantification was achieved using high performance liquid chromatography.
Results: NA and NX showed no statistically significant differential transport rates between the basolateral-to-apical (B-A) and apical-to-basolateral (A-B) directions and neither the influx nor the efflux were affected by the P-gp inhibitor.
Conclusion: NA and NX are not P-gp substrates. The differential intestinal absorption of the two opioid antagonists is P-gp independent and seems not to be related to a differential interaction with an intestinal transporter.

P189

Micro-cocktail validation for CYP3A and CYP2D6 assessment using a low dose of midazolam (0.075 mg) and dextromethorphan (2.5 mg)

Daali Y., Samer C., Eap C., Rebsamen M., Rossier M., Dayer P., Desmeules J. (Genève, Lausanne)

Background/Aim: Cocktail approach is generally preferred to individual administration of probes in order to characterize the activity of multiple enzymes. However, cocktail strategy has several drawbacks such as drug-drug interactions, tolerability and toxicity. Hence, there is a need to develop cocktails using low doses of probes. Our aim was to investigate whether the simultaneous oral administration of microdoses of midazolam (MDZ) and dextromethorphan (DEM) can be used to assess the simultaneous activities of CYP3A and CYP2D6.
Methods: As part of a 5 arm randomized cross-over control trial on the analgesic efficacy of oxycodone, ten healthy young non-smoking males received the following combinations of drugs: Quinidine (Q)+ ketoconazole (K) or Q+placebo (P) or K+P or P+P. In all cases MDZ (0.075 mg) and DEM (2.5 mg) were administrated 1 hour after Q, K or P. CYP2D6 and CYP3A activities were determined after urine collection during 8 hours (ratio DEM/DOR), and a blood sample (EDTA) after 30 min (ratio 1-OH-MDZ/MDZ). DEM and DOR analysis was performed using LC-fluorescence. MDZ and 1-OH-MDZ determination was performed using GC-MS. Allele's variants of CYP2D6 were detected using the AmpliChipTMCYP450 (Roche).
Results: CYP2D6 genotype predicted 1 poor (PM), 1 intermediate (IM), 7 extensive (EM) and 2 ultra rapid (UM) metabolizers. A good correlation was obtained between the predicted and the measured phenotypes except for 1 EM phenotyped as UM. Two duplications for alleles *41/*41xN and *1/*2xN were detected and the two volunteers were phenotyped as UM. A potent inhibition of CYP2D6 or CYP3A4 was obtained when Q or K were used. Mean metabolic ratio DEM/DOR in P and K groups were 0.015 (±0.028) and 0.015 (±0.019). It significantly increased in Q and QK groups (0.668 (±0.676) and 0.743 (±1.038)). Mean 1-OH-MDZ/MDZ in P, Q were 2.73 (±1.05) and 2.55 (±1.40) while it significantly decreased in K and QK groups (0.11 (±0.05), 0.10 (±0.05)). Moreover, there were no statistically significant differences between QK and K sessions for CYP3A and between QK and Q for CYP2D6 which indicate that there is no interaction between the two metabolic pathways.
Conclusion: Simultaneous assessment of CYP3A and CYP2D6 activities can be obtained by low oral doses (micro-cocktail) of MDZ and DEM. Specific inhibitors such as Q or K modulates selectively CYP2D6 or CYP3A activities.

P190

Kidney-related adverse drug reactions: results of a pharmacovigilance program in hospitalized patients

Zuliani E., Bertoli R., Cerny A. (Lugano)

Background: The standard classification of terms based on organ systems (CIOMS) does not account for ADRs in which the kidney is involved as a cause of an ADR. Hence we developed a new pathophysiologic classification of kidney-related ADRs and then applied it to the information in a pharmacovigilance database.
Methods: We retrospectively studied all cases of ADRs who have been submitted to the regional pharmacovigilance center by the internal medicine department of the Civico Hospital in Lugano between 01/2002 to 12/2005. We defined as kidney target any case in which the drug had a direct pharmacological effect on the kidney and this effect was responsible for the ADR. We classified as kidney cofactor the cases where the primary effect was not at the level of the kidney. We used standard statistical analysis tools.
Results: Among the 70 patients with kidney-related ADRs we identified 66% target and 34% cofactor cases. Electrolyte disorders were the most frequent type of kidney target ADR (85%), followed by AKI (48%). 96% of the cofactor cases had a GFR <60 ml/min/1.73 m^2. The patient with a kidney-target ADR tended to be an old woman, with AKI and/or an electrolyte disturbance, with ACEI/ARBs or diuretics causing the ADR. The patient with kidney-cofactor ADR tended to be an old man, with major hemorrhage or hypoglycemia from accumulation of a LMW heparin or a sulfonylurea, respectively. Using a definition of AKI based on a predetermined stepwise increase in serum creatinine, we identified 22 patients with drug-related AKI. When applying the RIFLE criteria to these patients, 18% did not qualify as AKI. None of these patients, as well as none of the patients that fell into the RIFLE renal "risk" category, needed renal replacement therapy. Since there were only 2 deaths related to drug-induced AKI, we could not draw any conclusions on the capacity of the RIFLE approach of predicting mortality.
Discussion: We analyzed the kidney-related ADRs by adopting a new patho-physiologic classification. Using the WHO classification for ADRs based on organ systems, some of the kidney-related ADRs would fall under other categories. We also took into consideration the cases in which the kidney had a major contribution to the development of ADRs, which allows to have a better estimate of the real burden of kidney-related ADRs. In spite of the low number of patients, there seemed to be a relationship between the RIFLE classification and the need for renal replacement therapy, whereas we could not find a clearcut relationship between this classification and outcome. Establishing the applicability of the RIFLE criteria to other patient populations, such as the population with drug-induced AKI, may prove useful.

P191

Catechol-methyl-transferase polymorphisms and pain sensitivity in fibromyalgia

Chabert J., Rebsamen M., Cedraschi C., Besson M., Matthey A., Chiappe A., Piguet V., Rossier M., Dayer P., Desmeules J. (Genève)*

Background and aims: Fibromyalgia (FM) is a chronic musculoskeletal pain condition. We previously demonstrated a state of central sensitization in FM using selective neurophysiological quantitative sensory testing (Nociceptive Flexion Reflex (NFR)). Some polymorphisms affecting the gene encoding catechol-O-methyltransferase (COMT) are associated with a reduction in the enzyme activity that influences pain regulation and anxiety and may participate in chronic painful diseases. Our aim was to evaluate the relation between COMT polymorphisms and quantitative sensory testing using NFR in FM as compared to a match control population.
Methods: 198 patients and 99 controls were included. The FM patients were asked to stop their centrally-acting analgesic treatment if they had one. 137 were classified as able to stop medication (ASM) and 61 as unable to stop medication (USM). Patients and controls were assessed for COMT genotype focused on 4 single nucleotide polymorphisms determined by TaqMan PCR: rs6269, rs4633, rs4818, and rs4680. Evaluation of pain thresholds was performed using the NFR.
Results: Most subjects were middle-aged females, with a 10 year mean duration of symptoms. Clinical measures indicated moderate to severe pain in both groups of FM. Psychosocial and functional aspects were severely affected in FM, USM group displaying worse results. Almost half of the ASM group was previously on central acting analgesics (antidepressant, opioid or anticonvulsivant medications) as compared to nearly all USM patients ($p < 0.001$). For COMT genotype, 3 major haplotypes were identified: ATCA (49%), GCGG (40%), ACCG (8%), that accounted for 97% of the seven detected. Those 3 haplotypes have been previously associated with different pain sensitivity levels: low (LPS), average (APS), or high (HPS) respectively. Six combinations of these 3 haplotypes were present. The number of LPS/LPS was significantly decreased in the USM group (4.9%) vs the ASM group (18.2%, $p = 0.003$) or controls (21.2%, $p = 0.007$). In ASM patients, a state of central sensitization was present in the majority of FM (71%) and the NFR of the LPS/LPS was significantly better compared to the others haplotypes (median 24.3 vs 21.3 $p < 0.05$).
Conclusion: COMT polymorphisms seems to be associated with the severity of neurophysiological and psychosocial consequences of FM and could contribute to account for a subgroup of FM patients prone to severe consequences of the disease.
Supported by the SNSF (NRP53–4049-405340-104645/1)

Adami M 58 S

Baerlocher GM 21 S
Ballmer PE 47 S
Berthoud M 6 S
Begré S 31 S
Berthold P 78 S
Bertoli R 77 S
Besson M 77 S
Bhattacharya I 25 S
Biedermann BC 41 S
Bloch J 5 S, 26 S, 54 S
Blum S 14 S
Bodenmann P 9 S, 56 S
Bochsler SC 46 S
Bonadies N 20 S
Bosshard W 8 S
Brauchlin AE 51 S
Britschgi A 20 S
Broz P 34 S
Buchkremer J 62 S

Calmy A 58 S
Carmona G 7 S
Carron PN 51 S, 58 S
Cedraschi C 61 S
Chabert J 80 S
Chapuis T 43 S
Chevalley T 7 S
Colucci G 68 S
Conte T 17 S
Conzett Th 60 S
Coutaz M 7 S
Curtin F 77 S

Daali Y 80 S
Damjanovic M 24 S
Dash C 61 S
de Beer D 15 S
Desmeules J 13 S
Depairon M 35 S
Dhayat N 68 S
Digon P 46 S
Donzé J 6 S
Dreher R 7 S
Dürr C 40 S

Egermann U 27 S
Elger BE 4 S
Escher M 61 S

Fassassi S 53 S
Faucherre M 55 S
Fausch K 44 S
Fayet A 78 S
Fehr R 57 S
Foerster M 9 S
Foglia R 55 S
Fontana E 23 S
Forestier M 69 S
Frank B 37 S

Franzen D 29 S, 35 S
Frasnelli ME 36 S
Frei P 49 S
Fretz G 50 S

Garcia E 22 S
Geismann FI 49 S
Gencer B 11 S
Goede JS 69 S
Gogos G 50 S, 51 S
Gonseth S 26 S
Guessous I 75 S
Gratwohl A 15 S
Gschwend S 11 S

Haas E 25 S
Haeuptle J 6 S
Hagmann N 33 S
Halter J 16 S, 65 S
Heim D 15 S
Heizmann M 65 S
Henzen C 23 S
Hirt A 19 S
Hodel Th 46 S
Hoess C 4 S
Hug BL 3 S
Hugli O 33 S
Humair JP 32 S
Hunziker S 55 S
Hutter A 49 S

Iff S 24 S
Imhof A 56 S

Jeger A 64 S
Jenal M 19 S
Joray S 76 S
Julmy F 73 S
Junod Perron N 13 S, 31 S

Kadi L 17 S
Kaiser P 57 S
Kanaan M 79 S
Käppeli S 31 S
Karathanasis S 52 S
Katz E 10 S
Keller P 70 S
Keller C 43 S, 44 S
Kindler V 19 S
Koeppel R 74 S
Kossovsky M 24 S
Kröger A 40 S

Lamoth F 59 S
Lamy O 38 S, 44 S
Lang PO 75 S
Lepori M 41 S
Levrat E 65 S
Liu T 20 S
Luthy C 13 S, 33 S, 75 S
Lutz HU 18 S

Madon J 73 S
Maile S 48 S
Manser CN 36 S
Maunz G 56 S
Marsteller I 53 S
Martina B 36 S, 45 S
Matter CM 12 S
Matthes T 14 S
Medinger M 17 S
Meier R 45 S
Merz K 39 S
Meyer BJ 34 S
Meyer SC 18 S, 21 S
Meyer-Heim T 28 S
Miedinger D 45 S
Moccetti M 38 S
Moret C 47 S
Motamed S 31 S
Müller C 54 S

Näf G 29 S
Nanchen D 12 S
Nguyen S 22 S
Nordmann AJ 3 S

Oberson M 37 S, 38 S
Ochs N 5 S
Oppliger Leibundgut E 19 S

Palhais N 3 S
Panchaud A 79 S
Pannatier M 39 S
Pasche A 29 S
Pascual A 60 S
Passweg JR 63 S
Penasa U 76 S
Perrig M 54 S
Perrottet N 78 S, 79 S
Peternac D 58 S
Peytremann Bridevaux 3 S
Pfister R 44 S
Piguet D 61 S
Piguet V 32 S
Pohl D 30 S
Potin M 34 S, 42 S
Pradier A 69 S

Rapin CH 75 S
Redondo M 68 S
Ribaudo G 57 S
Risch L 9 S, 11 S, 28 S
Rigamonti F 66 S
Righini M 11 S
Ritter S 27 S
Rivier E 33 S
Rochat Ph 49 S
Rochat S 8 S
Rodondi N 5 S
Roggero E 62 S
Roggo A 48 S
Rohacek M 59 S

Rothschild S 41 S
Rovó A 64 S
Rüfenacht U 24 S
Rüfer A 66 S
Ruggieri F 79 S
Rupprecht C 12 S

Sagmeister M 4 S
Sartori C 5 S
Schardt JA 20 S
Schaub F 14 S
Schiemann U 30 S
Schmid P 72 S, 73 S
Schmid S 48 S
Schmidtko J 71 S
Schoenenberger AW 4 S
Schreiber A 74 S
Schüpbach M 34 S
Semadeni GM 54 S
Senn L 56 S
Sigle J 71 S
Signorell L 52 S
Sladovnik P 40 S
Solenthaler M 66 S
Spahr N 22 S
Stähli C 39 S
Stalder M 16 S
Stempfle V 53 S
Stern M 63 S, 66 S
Studt JD 64 S
Sulger Büel E 10 S

Talamo Blandin A 62 S
Thaler Th 35 S
Thürlemann C 72 S
Tichelli A 70 S
Truong MH 42 S
Tschan MP 69 S
Tschudi M 18 S

Valsami S 70 S
Vetsch G 46 S, 52 S
Villaneau D 76 S
Vogt-Ferrier N 77 S
von Kietzell M 67 S

Waldvogel Abramowski S 67 S
Wasserfallen J-B 12 S
Weder C 42 S, 47 S
Weiss L 28 S
Widmer I 23 S
Wieland T 26 S
Willi C 9 S, 25 S
Wolber T 36 S

Zaugg D 42 S
Zehnder L 72 S, 74 S
Zimmermann S 37 S
Zuliani E 80 S